CARDIOLOGY
CURRENT PERSPECTIVES

Edited by

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UK

MARTIN DUNITZ

Cardiology
Current Perspectives

Dedication

Medicine is about sacrifices, and I know I have sacrificed sections of my family life that I will never recapture. My wife, Maggie, and children, Keira and Matthew, remain treasured.

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Preface

Perspective implies balance and the need to weigh up the various aspects of a given condition. Like a photograph constructed to portray an image seen through the eyes of the photographer, perspective also needs depth of field. This book is about perspectives seen through the minds of the authors who were charged with the task of writing about certainties and doubts and translating them into practicalities. You are invited to view each chapter in the same way that you would view a photograph – is the message clear, is the content complete, is there enough depth and is there still mystery? Mystery always has an appeal that documented fact lacks, but mystery from some will be self-evident to others. It follows, therefore, that this book cannot be all things to all readers, but that is not its purpose – to be something to most readers is the objective.

We live in a digital age and what is presented visually can easily be manipulated. When this book was in the planning stage I remembered and valued the honesty of the black and white photograph. I believe the authors have also – but where there are shades of grey no false colours have been introduced.

For 'current' read 'now', for 'perspectives' read 'judgements' for yourself. I hope you will read and feel it has been of value.

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Achieving Optimal Blood Pressure Control

Suzanne Wong, Kenneth Wong and Thomas MacDonald

Hypertension is very common within the population. The Framingham study highlighted a significant six-fold increased risk of stroke, a three-fold increase of cardiovascular death and a two-fold increase of peripheral vascular disease.[1] Hypertensive patients also have a six times greater risk of developing heart failure.[2] The Global Burden of Disease Study found that hypertension was the third most preventable cause of death worldwide, and the second most common in westernized societies.[3] Many studies have demonstrated that treatment of hypertension reduces morbidity as well as mortality. Hypertension is therefore a major cardiovascular risk factor amenable to prevention and intervention.

Although impressive improvement has been made since the 1970s in the management of hypertension, only 29% of hypertensive patients in 1988–1991 achieved the target pressure set as <140/90 mmHg.[4] Achieving target pressure is thus an important challenge to society and the health profession. However, optimal control of blood pressure (BP) is often difficult. Even in the setting of a large clinical trial, the Systolic Hypertension in the Elderly Program (SHEP), where the goal systolic BP was 140–160 mmHg, 28–45% of patients failed to achieve the goal pressure.[5] This chapter focuses on how to achieve optimal BP control.

Why do we need to lower blood pressure?

Blood pressure is normally distributed in the population and increases with age. The definition of hypertension is therefore arbitrary. The World Health Organization-International Society of Hypertension (WHO-ISH)[6] and the British Hypertension Society (BHS)[7] define sustained hypertension as BP persistently >140/90 mmHg. Isolated systolic hypertension is prominent in the elderly and is present if systolic BP exceeds 160 mmHg with a diastolic BP of <90 mmHg[8] (Table 1.1).

One of the problems with the management of hypertension is that the condition is usually asymptomatic until it manifests as a complication. Target organ damage can include cerebrovascular disease, myocardial infarction, heart failure, left ventricular hypertrophy, renovascular disease, peripheral vascular disease, aortic aneurysms or hypertensive retinopathy.

A 'modest rise' in BP in a population can enhance the risk of cardiovascular complications.[10] Both systolic and diastolic BP reductions have been associated with a reduction in stroke and cardiovascular endpoints,[11–13] and recently, pulse pressure has been recognized as important.[14] Each 5 mmHg reduction in diastolic BP is associated with a reduced risk of at least a quarter of end-stage renal disease.[15]

Up to the age of 79, there is evidence to suggest that a sustained systolic BP > 160 mmHg should be treated irrespective of the diastolic BP.[5,11] Lowering BP to normal in the hypertensive population does not reduce the cardiovascular risk to normotensive subjects.[16,17] Patients in the high risk group, but who are normotensive,[6] may still benefit from reduction of BP.

Threshold and target of BP control

In the management of hypertension, BP values should not be the sole determinant of initiation of treatment. The presence of other cardiac risk factors automatically places the patient at a higher risk level and this will determine the target pressure.[18–26] These risk factors include smoking, glucose intolerance, hyperinsulinemia, dyslipidemia, renal impairment, peripheral vascular disease, left ventricular hypertrophy and microalbuminuria (or albuminuria), high body mass index (BMI), age, sex and family history of premature cardiovascular disease. Anti-hypertensive treatment should be tailored according to overall reversible cardiovascular risks with the aim of achieving maximum reduction in the total risk of cardiovascular morbidity and mortality. The Joint British Society Coronary Heart Disease risk assessment program stratifies the hypertensive patient by absolute level of cardiovascular risk (Tables 1.1, 1.2).[9]

The BHS[7] and the WHO-ISH[6] recommend a target of <140/90 mmHg in most patients based on the Hypertension Optimal Treatment (HOT) study.[27] For patients with diabetes, a lower target of <130/85 mmHg is recommended by the WHO-ISH.[6] For those with existing cardiovascular disease or proteinuria, an even lower level is desirable. The existence of isolated systolic hypertension ≥160 mmHg is also worth treating in the elderly[5,11] In all these situations, even if the target is not achievable, any lowering of BP is beneficial after excluding non-compliance and secondary causes of hypertension.

Initial assessment of hypertension

Initial assessment should aim to identify opportunities of primary and secondary prevention of other cardiac risk factors, for end organ damage and to explain suboptimal BP

Category	*Systolic (mmHg)*	*Diastolic (mmHg)*
Normal	**<140**	**<90**
Mild hypertension	140–159	90–99
Moderate hypertension	160–179	100–109
Severe hypertension	≥180	≥110
Isolated systolic hypertension	≥160	<90

Table 1.1
Blood pressure levels: WHO-ISH definitions.[6]

Other risk factors and disease history	Mild hypertension	Moderate hypertension	Severe hypertension
No other risk factors	Low risk	Medium risk	High risk
1–2 risk factors	Medium risk	Medium risk	**Very high risk**
≥3 risk factors, */diabetes	High risk	High risk	**Very high risk**
**	**Very high risk**	**Very high risk**	**Very high risk**

Low risk = risk of cardiovascular event in next 10 years <15%;
Medium risk = risk of cardiovascular event in next 10 years 15–20%;
High risk = risk of cardiovascular event in next 10 years 20–30%;
Very high risk = risk of cardiovascular event in next 10 years ≥30%;
*target organ damage
**Associated clinical conditions, including cardiovascular and renal disease

Table 1.2
Stratification of risk in the hypertensive patient: Joint British recommendations.[9]

control, including both primary and secondary causes.

Assessment should include serum electrolyte and creatinine estimates. Abnormal renal function suggests the possibility of renal artery stenosis as a cause of hypertension, while high sodium and low potassium may reveal the diagnosis of hyperaldosteronism. Glucose and lipid profiles, including total cholesterol, HDL cholesterol and triglycerides, help to define cardiovascular risk more accurately. Gamma-GT is high in patients who consume large amounts of alcohol, which is a recognized cause of hypertension. TSH is high in hypothyroidism which can be associated with hypertension. Raised calcium may help to detect hyperparathyroidism, which is also associated with hypertension. The role of urinalysis has already been discussed. Twenty-four-hour urine collections for catecholamines are needed to exclude pheochromocytoma if subjects are symptomatic. ECG may detect evidence of myocardial ischemia or left ventricular hypertrophy (LVH). An echocardiogram should be considered in patients with an abnormal ECG or previous history of myocardial infarction, or current symptoms of cardiac disease to look for LVH and to assess systolic function. As it is well known that ECG criteria of LVH are not sensitive, it can be argued that all hypertensive patients should have an echocardiogram. There is also an argument to screen elderly hypertensive patients for aortic dilatation. Prophylactic surgery is indicated for an ascending aorta with a diameter of >6 cm.[28]

Nearly all outcome trials have been based on clinic BP and not on 24-hour ambulatory monitoring, (ABPM). However, ABPM is widely used. Through numerous measurements over a short period of time. ABPM reduces variability[29] and therefore correlates more closely with the risk of target organ damage and outcome.[30–32] ABPM is indicated in the following circumstances: unusual variability in BP, resistant hypertension

(>150/90 mmHg) despite three or more drugs, in the diagnosis of white coat hypertension, especially when symptoms suggest the possibility of hypotension. If ABPM is done, the average daytime BP is recommended by the BHS to be used for treatment decisions.[7]

Lightweight exercise testing has also been used to assess BP during submaximal exercise, as exercise systolic BP has been shown to be a better predictor of sustained hypertension than clinic BP.[33]

Controlling blood pressure

Non-pharmacologic

Non-pharmacologic means are recommended in all hypertensive patients. A weight loss of 3–9% can produce a 3 mmHg decrease in systolic and diastolic BP.[34] Exercise decreases overall cardiovascular risk. Alcohol consumption should be kept to British recommended levels of 21 units for males, 14 units for females.[7,35] Moderate alcohol consumption is also recommended.[36–38] Other lifestyle changes include cessation of smoking. The DASH diet (Dietary Approaches to Stop Hypertension) emphasized a diet of fruits, vegetable, low-fat dairy foods. This lowered BP by 5.5/3 mmHg compared to the control diet low in these ingredients with a fat content typical of the average diet in the USA.[39] Among the hypertensive group, the lowering effect was even greater (BP was lowered by 11.4/5.5 mmHg in the hypertensive group and by 3.5/2.1 mmHg in the normotensive group) as compared to the control diet. The DASH results support the earlier observation in the Treatment of Mild Hypertension Study (TOMHS) USA trial. Benefit was seen in BP control by dietary modification in mild hypertensive subjects (diastolic BP $\leq$99 mmHg) when treated with mono-drug therapy or placebo drug.[40,41] The recent DASH-sodium trial established that a reduction of sodium intake to levels below the current recommendation of 100 mmol/day in conjunction with the DASH diet lowers the BP with greater effect in combination than singly.[42] Compared with the control diet high in sodium intake, the DASH diet low in sodium level had a mean systolic BP of 7.1 mmHg lower in the normotensive population, and 11.5 mmHg lower in the hypertensive population.

Pharmacologic control of blood pressure

There is evidence that the major determinant of risk reduction with anti-hypertensive treatment is the lower BP achieved.[16,17] The choice of anti-hypertensives includes diuretics, beta-blockers, calcium antagonists, angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor antagonists, alpha-blockers, centrally acting drugs and spironolactone (not licensed in the UK for hypertension). The drug of first choice will depend on individual characteristics and co-existent diseases (see p. 7). The clinician must also consider the quality of life of the individual patient, rather than attempt to achieve an unrealistic target BP at the cost of intolerable side effects.

Essential hypertension is a heterogeneous condition and variability in individual subject responses to each drug group has been observed. What is the best strategy in treating patients who do not respond to the first drug? Some propose that the anti-hypertensive drug classes be rotated through systematically to achieve optimal BP control. This novel idea of

'treatment by crossover rotation' when used in young mild hypertensives (mean BP 161/98 mmHg) increased the proportion of patients achieving target BP (≤140/90 mmHg) on monotherapy from 39% to 73% ($p = 0.0001$).[43] This strategy of sequential therapy, instead of adding a second drug, has been tested and one trial showed that 57.7% of hypertensive patients reached a target diastolic BP <90 mmHg with initial single-drug therapy.[44,45] By changing to a second single therapy, 76% of those who failed with the initial drug managed to achieve target BP.[46]

Thiazide diuretics

Thiazides are inexpensive drugs for effective BP control. In the SHEP study of 1991, patients aged ≥60 years with isolated systolic hypertension treated with low-dose chlorthalidone reduced the incidence of total stroke by 36%, with 5-year absolute benefit of 30 events per 1000 participants.[5] In addition, major cardiovascular events were also reduced, with a 5-year absolute benefit of 55 events per 1000. Therefore, thiazides should be considered first choice unless there are relative contraindications like gout (hyperuricemia is a well-known side-effect of diuretics). There are other reasons why elderly patients in particular may find it difficult to use thiazide diuretics, for example those patients who suffer from urine incontinence or prostate problems.

The evidence is that low-dose thiazide reduces morbidity and mortality in stroke, coronary heart disease events and related mortality.[47,48] Higher dosage has not been shown to have more beneficial effect in lowering BP but instead increases the side-effects and metabolic disturbance.[49,50]

Beta-blockers

The 1992 MRC trial in the elderly was a placebo-controlled randomized trial, consisting of 4396 patients aged 65–74 with a follow-up of 5.8 years, which compared diuretics and beta-blockers.[47] Both treatments reduced BP compared with placebo. The diuretic group had significantly reduced risks of stroke (31%, $p = 0.04$), coronary events (44%, $p = 0.0009$), and all cardiovascular events (35%, $p = 0.0005$), while beta-blockers showed no significant reductions in these end-points. Thus beta-blockers should ideally **not** be used as the first-line treatment in this age group,[51,52] but can be used as an alternative or supplementary therapy to diuretics.[53] The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[54] and Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)[55] are awaited to elaborate further the comparative treatment from combinations of antihypertensives.

Calcium antagonists

Long-acting antagonists are inexpensive and successful in lowering BP.[56] They also have mortality benefits in reducing the rate of fatal and non-fatal stroke and the rate of cardiovascular events in both hypertension[57] and isolated systolic hypertension.[11] They can be used as alternatives to thiazide diuretics or in combination with others. The International Nifedipine GITS Study of Intervention as a Goal in Hypertension Treatment (INSIGHT) is the first prospective study to investigate whether the benefits of the older diuretic antihypertensive drugs are similar to newer drugs like calcium antagonists.[58] Long-acting nifedipine was as effective as co-amilozide in lowering BP and preventing overall cardiovas-

cular or cerebrovascular complications among a cohort of 6321 middle-age to elderly (55–80 years) hypertensive patients with ≥1 cardiovascular risk factor.

However, short-acting dihydropyridine calcium antagonist (nifedipine) should be avoided due to reported fears of increased risk of mortality and myocardial infarction.[59,60]

ACE inhibitors

ACE inhibitors reduce cardiovascular mortality and morbidity after myocardial infarction when left ventricular failure (LVF) is present[61] and are specially indicated as first-line therapy in patients with type I diabetes,[62] proteinuria or left ventricular dysfunction.[63] The Heart Outcomes Prevention Evaluation (HOPE) study showed that high-risk patients also benefit from ramipril with a reduction in stroke (31%) and myocardial infarction (20%).[64] ACE inhibitors are similar to calcium channel blockers or conventional drugs (beta-blockers or diuretics) in preventing cardiovascular mortality.[53]

It is important to remember that ACE inhibitors are relatively contraindicated in renal artery stenosis and it is good practice to check the patient's renal function one week after commencement.

Angiotensin II receptor antagonists

Angiotensin II receptor antagonists are extraordinary for their placebo-like adverse effects. They are recommended as alternatives to ACE inhibitors when side-effects such as cough are not tolerated. There are no trials that demonstrate their effects in mortality or morbidity. No outcome studies have been completed in hypertension but the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial,[65] SCOPE,[66,67] and Losartan Intervention For Endpoint reduction in Hypertension (LIFE)[68] studies are in progress. In heart failure, the ELITE II study showed no difference in mortality between captopril or losartan in subjects with chronic heart failure.[69] The Valsartan Heart Failure Trial (VALHEFT)[70] also failed to show a mortality benefit of valsartan when added to optimal treatment of heart failure but did show that valsartan reduced hospitalization for heart failure, especially in those who were ACE inhibitor intolerant or could not take beta-blockers.

Alpha-blockers

Alpha-blockers are recommended as alternative or supplementary treatment for hypertensive patients. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends alpha-blockers as a possible first-choice drug, especially if dyslipidemia and or prostatism are present.[71] In January 2000, the doxazosin limb of the ALLHAT study was stopped early by the ALLHAT Data and Safety Monitoring Board. The interim analysis of the 24 000 patients who had a mean follow-up of 3.3 years showed that, when compared to patients receiving chlorthalidone, those receiving doxazosin had a significant 25% increased risk of combined cardiovascular disease event including a two-fold increase of congestive heart failure.[72] Both groups were however, equally likely to develop the primary outcome of fatal coronary heart disease and nonfatal myocardial infarction. This led to the cautionary use of doxazosin as monotherapy treatment in hypertensive patients. However, the absence of a placebo group in the trial does not establish how the congestive heart failure rate with

doxazosin would compare with no antihypertensive treatment, only that chlorthalidone is superior to doxazosin.

Centrally acting and vasodilator drugs

In refractory hypertension, or in subjects who have difficulty tolerating side-effects, centrally acting drugs like moxonidine, and vasodilators like minoxidil, can be tried. Methyldopa remains a good choice in hypertensive patients who are pregnant. Centrally acting drugs are also safe in asthmatics and heart failure. Keeping the daily dose of methyldopa below 1 g minimizes side-effects.

Spironolactone

Spironolactone has proven mortality benefit in patients with severe heart failure.[73] It is also indicated as first-line or additive agent in aldosteronism. It is not licensed for hypertension in the UK but is used extensively in other countries. Even quite low doses, such as 12.5 mg spironolactone, can be effective in resistant hypertension (see 'Primary hyperaldosteronism', p. 13). However, the full effects may take up to 3 months to become apparent.

The BP response to ACE inhibitors and beta-blockers was shown to be strongly correlated, as was the BP response to calcium antagonists and diuretics. In young hypertensives, we would recommend starting a beta-blocker or ACE inhibitor in the first instance, and if target BP is not achieved, then change to either a diuretic or calcium antagonist instead. In the older hypertensive patient, the evidence is in favour of starting with a diuretic or long-acting calcium antagonist first, and if that is unsuccessful, then change to an ACE inhibitor or to a beta-blocker. The choice of antihypertensive treatment is, however, clearly dependent on the presence or absence of compelling indication or contraindication in the individual patient.

Blood pressure control and co-existent disease

Diabetes mellitus

The prevalence of hypertension in patients with diabetes mellitus is approximately 1.5–2.0 times greater than in an appropriately matched non-diabetic population.[74]

Type 2 diabetes

Non-insulin dependent diabetes mellitus is now regarded as a cardiovascular disease. Tight control of hypertension has been shown to lower the risks of cardiovascular complications and retinopathy in the HOT study[27] and UK Prospective Diabetes Study (UKPDS).[75]

In the HOT study, the lowest incidence of major cardiovascular events occurred at a mean achieved diastolic BP of 82.6 mmHg, while the lowest risk of cardiovascular mortality occurred at 86.5 mmHg. In patients with diabetes mellitus there was a 51% reduction in major cardiovascular events in target group $\leq$80 mmHg compared with target group $\leq$90 mmHg ($p = 0.005$).[27]

The UKPDS had a BP limb that aimed to determine whether tight control of BP would prevent macrovascular and microvascular complications in patients with NIDDM.[72] In this large randomized controlled trial, the aim of tight BP control was <150/85 mmHg with the use of captopril or atenolol as the main treatment. A comparative group with less tight BP control aimed at <180/105 mmHg. The study followed 1148 hypertensive patients with NIDDM whose mean age was 56 and whose mean BP was 160/94 mmHg at entry.

Of these, 758 patients were allocated to tight BP control (achieved mean BP 144/82 mmHg), and 390 patients to less tight BP control (achieved mean BP 154/87 mmHg) with a median follow up of more than 8 years. The mean BP during follow up was significantly reduced in the group assigned tight BP control compared with the group assigned to less tight control ($p < 0.0001$). The group with tight BP control had a 24% reduction in diabetes-related end-points ($p = 0.0046$), 32% reduction in diabetes-related deaths ($p = 0.019$), 44% reduction in strokes ($p = 0.013$), and 37% reduction in microvascular end points ($p = 0.0092$). There was a non-significant reduction in all-cause mortality. Therefore, it is clear from the UKPDS that tight BP control in patients with hypertension and NIDDM reduces the risk of macrovascular complications, including deaths and strokes.

What is the antihypertensive drug of choice in type 2 diabetes? ACE inhibitor and beta-blocker-based therapeutic regimes were equally effective in reducing mortality in the UKPDS trial.[62] Whilst many practitioners may have concerns about prescribing beta-blockers to diabetic patients for fear that it might mask or prolong the symptoms of hypoglycemia, the UKPDS reported that the proportion of patients with hypoglycemic attacks was no different between groups. However, the mean weight gain in the atenolol group was greater (3.4 kg compared to 1.6 kg).

Interestingly, there is evidence that beta-blockers may actually promote glucose intolerance. Gress' recent cohort study of 12 550 non-diabetic adults studied the independent relationship between the use of antihypertensive medication and the risk of subsequent type 2 diabetes.[76] After adjusting for potential confounders, it was found that hypertensive patients on thiazide diuretics, ACE inhibitors or calcium antagonists did not have a greater risk of developing diabetes compared to those who did not receive any anti-hypertensive therapy. However, there was a 28% higher risk of developing diabetes for those taking beta-blockers compared to those who did not receive any antihypertensive therapy.[76] This evidence needs to be weighed in proportion against trials showing that beta-blockers decrease morbidity and mortality. Also ramipril, an ACE inhibitor, has been noted to decrease the rate of development of diabetes by 30% in the HOPE cohort of patients. A combination of ACE inhibitors and beta-blockers may abrogate the adverse effect of beta-blockers with respect to diabetes.[64] Until such evidence arrives however, beta-blocker use in hypertensive patients who have diabetes and who have a high prevalence of underlying coronary heart disease will continue to have an important therapeutic role.

The calcium antagonist-based regime in the HOT study also appeared to be effective in the reduction of cardiovascular events. This provides additional support to evidence from Syst-Eur suggesting that nitrendipine is of benefit in diabetic patients.[11] However, ACE inhibitors probably remain the drug of choice over calcium channel blockers in view of the results from the ABCD trial, which was terminated prematurely when it emerged that the risk of myocardial infarction in patients randomized to nisoldipine was significantly greater compared with those randomized to enalapril.[77] It should be noted that this finding was based on a secondary-endpoint. Furthermore, it was unclear whether the excess risk was due to the protective effect of enalapril or a true detrimental effect of nisoldipine.

Previously, diuretics were regarded as con-

traindicated in diabetes. However, new evidence has emerged indicating that thiazides improve prognosis substantially.[48] Therefore, low-dose thiazides are now recommended as second-line treatment in NIDDM.

Clinicians often find that in order to achieve tight control of hypertension in diabetic patients, it is necessary to use polypharmacy, which clearly has potential problems, especially in the elderly population with side-effects and non-compliance.

In the UKPDS, after 9 years of follow-up, 29% of patients in the group assigned to tight control required three or more medications to lower BP to achieve the target of <144/82 mmHg.[72]

Finally, it should be emphasized that other cardiovascular risk factors should be carefully controlled in diabetics. Glycemic control should also be optimized. Patients should give up smoking and statin treatment is often indicated. Simvastatin and atorvastatin have, in addition to their cholesterol-lowering actions, anti-oxidant effects. Interestingly, a recent study by Tonolo et al showed that simvastatin reduced both the BP and 24-hour urinary albumin excretion in a group of 26 microalbuminuric hypertensive type 2 diabetics.[78] This effect was independent of the LDL cholesterol effect. Aspirin should be considered in all patients over 50 years of age at a high risk, with BP controlled at <150/90 mmHg unless there are contraindications.[7]

Type 1 diabetes

The target BP in type 1 diabetes is even lower than in type 2 diabetes. We should aim for a target BP of less than 130/80 mmHg.[27] In patients with proteinuria >1 g/24 hours, the target is <125/75 mmHg.[79]

Optimal BP control protects renal function. BP reduction and ACE inhibitors can slow the decline in renal function in overt diabetic nephropathy.[80] ACE inhibitors appear to delay progression from the microalbuminuric phase to overt nephropathy.[81–83] Therefore, ACE inhibitors are recommended as first-line therapy for hypertension in patients with type 1 diabetes with nephropathy.

Ischemic heart disease

Beta-blockers and ACE inhibitors are drugs of choice for hypertensive patients with known ischemic heart disease.

The HOPE study was terminated early because of a clear reduction in cardiovascular deaths in patients with coronary artery disease taking ramipril.[64] Importantly, these patients were not known to have heart failure. (ACE inhibitors are well known to reduce mortality in patients with heart failure.)

In addition to treating hypertension, other drugs that reduce cardiovascular risk must also be considered. These include aspirin for secondary prevention of cardiovascular disease, and primary prevention in treated hypertensive subjects over the age of 50 years who have a 10-year coronary heart disease risk $\geq$15% and in whom BP is adequately controlled. Statin therapy is recommended for hypertensive people with a total cholesterol $\geq$5 mmol/L and established vascular disease, or 10-year coronary heart disease risk $\geq$30% estimated from the Joint British Societies' coronary heart disease risk chart, although some argue that lower risk subjects should also be treated. Glycemic control should also be optimized in diabetic subjects.[7]

Aortic regurgitation

ACE inhibitors and nifedipine reduce afterload and regurgitant volume in patients with aortic regurgitation.

Cerebrovascular disease

BP reduction is recommended for the primary prevention of stroke and transient ischemic attacks (TIA). Further, BP reduction among hypertensive patients with a previous history of stroke produced a 29% reduction in stroke risk and a trend towards reduction of coronary heart disease risk.[84]

However, in the acute stroke setting, BP is often elevated and unstable for a few days. There is evidence to suggest that lowering BP in this phase may be harmful, possibly because lowering BP reduces the effectiveness of autoregulation of cerebral blood flow and hence reduces cerebral perfusion. Therefore, antihypertensive therapy is not generally recommended in the early days after an acute stroke.

On the other hand, BP lowering after acute stroke may be appropriate in the following circumstances. First, primary intracerebral hemorrhage, second, if the stroke occurs as a result of accelerated hypertension and third, after subarachnoid hemorrhage (when nimodipine should be used because of its effects in reducing unfavorable outcomes from cerebral vasospasm).

In the light of the PROGRESS trial (Perindopril pROtection aGainst REcurrent Stroke Study (not yet published), the drugs of choice for lowering blood pressure in neurologically stable patients who suffered a stroke or TIA (up to five years ago) are perindopril and indapamide.

Depression

Beta-blockers and centrally acting sympatholytics (e.g. methyldopa) should be avoided in patients with depression.

Renal disease

Hypertensive patients with abnormal renal function and or proteinuria should be referred for specialist evaluation. BP should be controlled in hypertensive patients to reduce the progression of renal disease. The target BP for patients with renal impairment or persistent proteinuria is <130/85 mmHg. Patients with renal disease and proteinuria >1 g/24 hours should have BP controlled to 125/75 mmHg (see 'Type 1 diabetes', p. 9).[79]

In the absence of renal artery stenosis, the anti-hypertensive drug of choice in patients with renal failure is an ACE inhibitor. In a meta-analysis published in 2000, Kshirsagar et al showed that treatment of chronic renal insufficiency with ACE inhibitors delayed the progression of disease compared with placebo.[85] This observation held for individuals with renal insufficiency of various causes and over a spectrum of disease severity. Thiazides are less effective in the presence of renal failure with creatinine level >150 μM. Loop diuretics should be used in patients with signs of fluid overload. It must be remembered that the dose of those anti-hypertensive drugs excreted by the kidney may need to be adjusted.

Urea and creatinine should be checked within 1–2 weeks of commencing antihypertensive therapy, especially ACE inhibitors or angiotensin II antagonists. If serum creatine is raised, renal artery stenosis should be considered as a possibility and the patient should be referred to a nephrologist for further inves-

tigations, such as doppler ultrasound of the renal arteries, MRI angiogram, or the gold standard, renal angiography.

Renovascular disease

Renal artery stenosis is an infrequent cause of hypertension (1%), but is more common in older people.[86] Renal artery stenosis should be suspected in the following clinical scenarios:

- Malignant hypertension, resistant hypertension (despite triple therapy) in the presence of other indications.
- Renal impairment of unknown cause, especially with little or no proteinuria.
- Inequality of renal size on ultrasound.
- Elevation of serum creatinine by ACE inhibitor or angiotensin II receptor antagonist.
- Peripheral vascular disease or severe generalized atherosclerotic disease.
- Recurrent pulmonary edema.
- Young women with hypertension (fibromuscular dysplasia).

The drugs of choice in renal artery stenosis are calcium antagonists and alpha-blockers. The patient should be considered for renal angioplasty and stenting as this has been shown to be the most effective treatment for aorto-ostial lesions.[87] However, some clinicians argue for good BP control with medication, as stenting is in general unproven. The recent study by van Jaarsveld et al compared angioplasty with drug therapy in patients with $\geq$50% renal artery stenosis and uncontrolled hypertension showed that angioplasty had little advantage over drug therapy at 12 months.[88] However, there was a 49% treatment crossover of patients from the drug to angioplasty treatment group which may have diluted and influenced the results in this group.

Pregnancy

Hypertensive women who plan pregnancy, or who have become pregnant whilst on antihypertensive treatment, are advised to change their therapy to one of the drugs recommended for the treatment of hypertension in pregnancy. It is usual to switch from such agents back to the previous antihypertensive treatment after delivery.

Methyldopa remains the antihypertensive drug of choice for idiopathic hypertension or pre-eclampsia[7] because of its long and extensive use without reports of serious adverse effects on the fetus. Second-line drugs include nifedipine, hydralazine, and labetalol. Labetalol has both alpha- and beta-blocking effects and is widely used as a second-line agent particularly for resistant hypertension in the third trimester. Other beta-blockers are used less often, especially before 28 weeks' gestation, owing to concerns that they may inhibit fetal growth. Atenolol given from the end of the first trimester in patients with mild hypertension is associated with intrauterine growth retardation.[89] ACE inhibitors and angiotensin II antagonists should be avoided because they may cause oligohydramnios, renal failure, hypotension and intrauterine death in the fetus.

Patients aged 80 and over

Physiological changes in aging render the elderly more susceptible to hypotension as a result of therapy, rapid changes of posture or

disease. The addition of declining mental function in some makes compliance difficult. Alterations in drug pharmacokinetic and risk of side-effects also need to be taken into account.

The European Working Party on High BP in the Elderly (EWPHE) study included 155 patients over 80 years of age (maximum 97 years old).[90] The STOP study recruited 269 patients over 80 (up to 84 years old).[91] Neither study showed any benefit from treatment of patients over the age of 80. However, the small numbers were insufficient to exclude the possibility of an advantage. In the SHEP study,[5] 649 patients over 80 years old took part, and treatment of isolated systolic hypertension was associated with a 45% reduction of incidence of stroke.

The INDANA group collected data from all participants aged 80 years and over in randomized controlled trials of antihypertensive drugs.[92] The primary outcome was fatal and non-fatal stroke. Secondary outcomes were death from all causes, cardiovascular death, fatal and non-fatal major coronary and cardiovascular events, and heart failure. The study found 57 strokes and 34 deaths among 874 actively treated patients, compared with 77 strokes and 28 stroke deaths among 796 controls, representing one non-fatal stroke prevented for about 100 patients treated each year. The meta-analysis of data from 1670 participants aged 80 years or older suggested that treatment prevented 34% of strokes. Rates of major cardiovascular events and heart failure were significantly decreased by 22% and 39% respectively. However, there was no treatment benefit for cardiovascular death, and a non-significant 6% relative excess of death from all causes. The inconclusive findings for mortality contrast with the benefit of treatment for non-fatal events. Results of a large randomized controlled trial are needed for definite conclusion that antihypertensive treatment is beneficial in patients with hypertension aged 80 and over.

The Hypertension in the Very Elderly Trial (HYVET) is a multicenter, open, randomized and controlled trial.[93] The aim of this trial is to investigate the effect of active treatment on stroke incidence in hypertensive patients over the age of 80 years. Secondary end-points include total cardiovascular mortality and morbidity. Entry criteria include a sustained sitting systolic BP of 160–219 mmHg plus a sustained sitting diastolic BP of 95–109 mmHg. Also required is a standing systolic BP of $\geq$140 mmHg. Patients must be free of congestive heart failure requiring treatment, gout, renal failure or a recent cerebral hemorrhage. Patients are to be randomized to 3 groups: no treatment; treatment with a thiazide diuretic; or treatment with lisinopril (5 mg daily). Slow release diltiazem (120 mg/day, increasing to 240 mg/day if required) may be added to the medication of the actively treated groups.

Until the results of this study become available, an age threshold beyond which hypertension should not be treated cannot be justified. However, clearly the decision to treat or not has to be made on an individual basis, taking into account the comorbidities of the individual patient and whether potential side-effects are acceptable. The patient's mental state must of course also be taken into consideration.

Hypertensive emergencies

Severe hypertension (diastolic BP > 140 mmHg), or malignant hypertension (grades 3 or 4 retinopathy) and hypertensive heart failure, are

medical emergencies and require immediate hospital admission for treatment, as they can cause rapid loss of renal function. Malignant hypertension is rare. Survival is greatly improved with treatment, from 10% 5-year survival to 80% 5-year survival.[94]

Immediate treatment is required, but parenteral therapy is normally avoided for fear that an over-rapid reduction in BP at a time when auto-regulation of cerebral blood flow is compromised may lead to acute cerebral or retinal infarction. Oral therapy producing a gradual fall in BP over 3 days is normally sufficient. As a result, two drugs should always be given orally initially, one of which should be a diuretic.

Indications of parenteral treatment include the following clinical scenarios:

- Hypertension with LVF; iv glyceryl trinitrate or sodium nitroprusside may be helpful.
- Aortic dissection: iv sodium nitroprusside is the agent of choice.
- Hypertensive encephalopathy (fluctuating neurological signs usually associated with advanced retinopathy, commonly occurring when hypertension has developed over a relatively short time – e.g. hypertension of pregnancy, renovascular hypertension, scleroderma renal crisis, acute nephritic syndrome: the agent of choice is iv sodium nitroprusside. Even in this context, it is not advisable to lower diastolic BP too quickly in the first 24–48 hours.

Resistant hypertension

First and foremost, it is important to seek any reversible cause, such as poor compliance to recommended therapy, alcohol excess, and secondary hypertension, e.g. renal artery stenosis. Importantly, drugs that potentially can cause hypertension, such as non-steroidal anti-inflammatory drugs, cyclosporin, sympathomimetics, antidepressants and steroids should be discontinued if possible.

Non-compliance can be difficult to exclude objectively. Electronic compliance monitoring has been shown to improve BP control significantly at 2 months without change to treatment.[95] BP became normal in a third of the patients and insufficient compliance was unmasked in a further 20%. This can be a reliable and objective method of measuring drug compliance to provide rational modification of treatment in genuine refractory hypertension and to optimize BP control with more potent regimes of combination therapy.

White coat hypertension frequently leads the unwary clinician to increase antihypertensive medication. Diagnosis requires a 24-hour ambulatory BP monitoring.

Primary hyperaldosteronism

Hypertensive patients who have resistant hypertension despite multiple drug therapy may have primary hyperaldosteronism. Hyperaldosteronism used to be diagnosed by metabolic changes including hypokalemia and alkalosis with resistant hypertension. However, it is now known that the majority of subjects are normokalemic.[96] The confirmatory test is the failure of plasma aldosterone suppression in response to salt loading and or fludrocortisione.[97] Hyperaldosteronism due to an aldosterone-producing adenoma is rare, however bilateral idiopathic hyperaldosteronism is increasingly diagnosed.[98] Studies using an aldosterone-renin ratio of >750 as a diagnostic criterion suggest that primary hyper-

aldosteronism may be as prevalent as 10–20% among the hypertensive population, both in hospital and primary care setting.[99,100] Spironolactone, an aldosterone antagonist, is probably the first treatment for primary hyperaldosteronism.[101] In Lim et al's study of 28 patients with primary aldosteronism, 48% achieved BP control ≤140/90 mmHg and 48% were treated with spironolactone therapy alone.[102] Other treatments appear less effective. The value of eplerenone in BP control is being tested in trials. It is a more selective competitive aldosterone receptor antagonist offering the promise of less anti-androgen side effects.

Combination therapy

Most hypertensive patients will require a combination of antihypertensive drugs to achieve optimal BP control.[27,75] Combination therapy potentially offers the benefit of fewer side-effects, because lower doses of each drug may be given compared with monotherapy.

Logical and effective combinations include, for example, ACE inhibitor plus diuretic (especially in patients with evidence of fluid overload secondary to LVF); beta-blocker plus diuretic; or beta blocker plus calcium channel blocker (dihydropyridines only). A regime for the treatment of genuine refractory hypertension needs to target different mechanisms of BP control, e.g. calcium channel blocker plus ACE inhibitor plus loop diuretic. Spironolactone is effective in primary hyperaldosteronism but not licensed for hypertension alone in the UK.

Conclusion

Optimizing BP control is important for prognosis. Pooled results from nine prospective observational studies indicate a prolonged difference in usual diastolic BP of 5 mmHg, 7.5 mmHg and 10 mmHg were respectively associated with at least 34%, 46% and 56% less stroke and at least 21%, 29% and 37% less coronary heart disease.[10] Trials of drug treatment in hypertension showed that for a drug-induced fall in diastolic BP of 5–6 mmHg, the incidence of stroke was reduced by 38% and coronary heart disease by 16% in patients with mild hypertension.[103] There is now evidence and opinion to support a target reduction of BP to 140/90 mmHg in the general population, 130/80 mmHg in diabetics and 125/75 mmHg in renal patients with proteinuria of >1 g/24 hours. Optimal BP control requires careful selection of therapy for the individual patient, for example ACE inhibitor therapy for the diabetic who has no contraindications to the drug. Importantly, other risk factors of cardiovascular disease need to be controlled. Patient compliance is likely to improve with once a day medication and through better communication from physicians about possible side-effects, especially when the patient has not had any symptoms. Clinical governance is becoming increasingly important, and there is a wealth of evidence to support control of BP, with clear guidelines on the management of hypertension, including audit standards.[7] Physicians need to make conscientious efforts in partnership with patients to optimize BP control.

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2

Regression of Left Ventricular Hypertrophy

M Mitchell Lindsay and Francis G Dunn

Introduction

Patients with hypertension who also have left ventricular hypertrophy (LVH) constitute a particularly high-risk group who are therefore likely to derive particular benefit from optimal antihypertensive therapy. This strategy of identifying patients in high-risk sub-groups is applied over a series of situations in clinical medicine, with another obvious example being the aggressive treatment of hypercholesterolaemia in patients with coronary heart disease. If there is doubt about the need to treat borderline hypertension then the presence of LVH strengthens the case for treatment. The following issues will be addressed in this chapter.

- Why is the presence of LVH such an important finding in patients with hypertension?
- What factors contribute toward the increased risk of LVH?
- What factors control the development and progression of LVH?
- Does regression of LVH occur and what is the optimal blood pressure level?
- Do antihypertensive drugs differ on their ability to promote this regression?
- Is there any evidence that regression of hypertrophy is clinically important?

The importance of LVH

Sir Thomas Lewis described graphically in his classic monograph the mode of death in patients with hypertension.[1] It was not, as might have been expected, from myocardial infarction or cerebrovascular accident, but from progressive heart failure consequent upon the unrelenting development of LVH with no effective method of off-loading the ventricle. It is therefore not surprising, if underemphasized, that all major antihypertensive trials have shown a substantial reduction in death from hypertensive heart failure. However despite this reduction in hypertensive heart failure, LVH still constitutes a major cardiovascular risk factor.

Much of the information on LVH as a risk factor comes from the Framingham study which was set up in the late 1940s to follow up a large cohort of healthy adults and to identify factors of risk for subsequent cardiovascular morbidity and mortality.[2] The authors used the ECG as a means of identifying LVH. In those early years this proved to be an effective screening investigation. This study showed that the presence of definite LVH (defined as ECG voltage criteria plus ST-T change) doubled the risk of cardiovascular disease in comparison to hypertension alone. This increased risk could not be

explained on the basis of age, sex, level of blood pressure or other associated risk factors. The importance of LVH as a risk factor for coronary artery disease is even more striking, with a two to three fold increase in the number of myocardial infarctions when LVH is present on the ECG. Sudden death is increased by a factor of five. LVH is an independent risk factor for sudden cardiac death in men independent of the presence of coronary disease, although a less clear cut relationship was seen in women.[3]

The Framingham findings were confirmed in a large study from Glasgow which assessed the implications of ECG LVH.[4] This study showed an increased risk, associated with definite LVH but, in addition, voltage LVH (known in the Framingham study as possible LVH) was shown to carry an increased risk which could not be explained on the basis of BP alone.[4] The risk was greater in men at all levels of BP, and was considerably magnified by smoking.

It has been known for a number of years that the ECG diagnosis of LVH has limitations in terms of both sensitivity and specificity. Therefore the question arises as to whether there is a cohort of patients who actually do have LVH despite a normal ECG and who are at increased risk. The advent of echocardiography has permitted this question to be addressed, since it is a more sensitive and specific method of assessing LVH than the ECG.[5] Echocardiography has the added advantages of assessing cardiac function and more accurately following changes with time. It has also been shown that echocardiographic LVH is an important prognostic factor for the cardiovascular complications of hypertension,[6,7] and is a better predictor of the risk of fatal and non-fatal events than the BP.[8] Echocardiography also has shortcomings in its inability to provide information on all patients and also because of the variability of left ventricular mass (LVM) measurement during serial assessment. An important study has shown that despite excellent variability, with an interclass co-efficient of 0.86, the 95% confidence interval with a single replicate measure of left ventricular mass is 59 g.[9] This exceeds the usual decrease in mass during treatment.[10] That is not to say that with a large cohort of patients, meaningful results cannot be achieved, since the width of a population confidence interval decreases proportionally with the inverse of the square root of the sample size. Hence, although the confidence interval for changes in left ventricular mass for a single patient is 59 g, in 50 patients it would be $59\ g/\sqrt{50}$ or 8.4 g.

Unfortunately in many of the clinical studies the number of patients involved is rather small; which makes it difficult to interpret the significance of the findings. Problems with interstudy variability also applies to tests of diastolic function, although the ejection fraction has a narrower confidence interval.

Radionuclide estimates of left ventricular function can be performed on all patients and therefore have an advantage over echocardiography. Serial measurements of ejection fraction have been used in a number of studies and have provided useful information. However, this technique would clearly not be appropriate in the clinical management of patients with hypertension. Studies of magnetic resonance imaging indicate that this technique is superior to the echocardiography in the measurement of LV mass with improved reproducibility.[11–14] MRI may therefore be of value in providing definitive information on regression of LVH in clinical research studies. As with radionuclide imaging, the widespread

use of this technique on a clinical basis is not practical at the present time.

Contributing factors to increased risk of LVH

Several different factors have been postulated as causing or contributing to the increased risk associated with LVH (Fig. 2.1), but it is first necessary to understand the pathophysiological background to LVH. The heart hypertrophies in response to elevation in the left ventricular wall stress, which occurs as a consequence of hypertension. Cardiac muscle hypertrophy initially serves to return wall stress to normal, thus preserving left ventricular systolic function and reducing the likelihood of myocardial perfusion abnormalities. This adaptive response is limited, however. If systolic blood pressure remains elevated cardiac function and myocardial perfusion will eventually deteriorate. Despite the apparently protective role of LVH, in the long-term, it causes a number of pathophysiological abnormalities. All of which could contribute to its adverse prognostic profile.

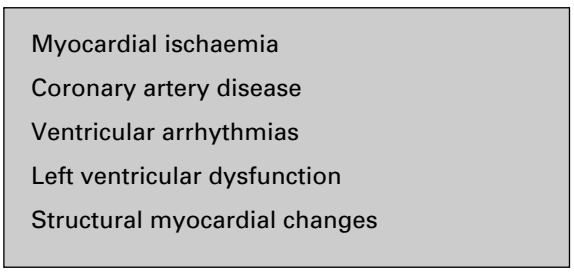

Figure 2.1
Factors contributing to the risk associated with LVH in patients with hypertension.

Myocardial ischemia

Several factors are involved in the development of myocardial ischemia in hypertension and LVH. Hypertension enhances the development of atherosclerosis and also induces specific changes in the coronary circulation.[15] This consists of an increase in the media:lumen ratio, a consequent decrease in the lumen size and additional functional changes in the vessels.

Additionally, angina has been shown to occur in hypertensive patients in the absence of documented coronary disease.[16] Part of the explanation for this is the increment in myocardial workload determined by the systolic BP[17] and also the likely imbalance of oxygen supply and demand in the presence of LVH. Key factors leading to this imbalance are abnormalities in coronary vasodilatation,[18] impairment of coronary flow reserve[19] and abnormal coronary vasomotor responses.[20]

Thus, even in the absence of overt coronary disease, the combination of hypertension and LVH provides an ideal template for the development of myocardial ischemia. In a study of 90 patients with ECG LVH who underwent 24 hour holter monitoring, 43 had ST segment depression of which 90% were clinically silent.[21] In addition, 26 patients had a positive exercise test and 48 patients had reversible defects on thallium scanning. Thus both symptomatic and silent myocardial ischemia are common findings in patients with LVH, even in the absence of epicardial coronary disease.

Ventricular arrhythmias

LVH is associated with both an increase in sudden death and in ventricular arrhythmias assessed by Holter monitoring.[6,22,23] This has

demonstrated an increased frequency and complexity of ventricular ectopy in patients with LVH.[23,24] However no clear relationship between these dysrhythmias and sudden death has been demonstrated.

Animal studies have revealed multiple electrophysiological abnormalities which may help explain the incidence of arrhythmias in hypertensive patients. These include increased vulnerability to ventricular arrhythmia,[25] dispersion of monophasic action potential duration[26] and refractoriness and action potential prolongation.[27] Despite this wealth of laboratory data and observational studies, there is no direct experimental evidence that demonstrable ventricular ectopy leads to complex ventricular arrhythmias and consequent sudden death. Indeed studies using both late potential and invasive electrophysiological stimulation have failed to show any increment in the propensity for the inducement of reentrant ventricular dysrhythmias.[28] A more likely explanation for the ventricular ectopy is that it reflects myocardial ischemia which may be a contributing factor to the increment in sudden death.

Systolic/diastolic dysfunction

Hypertension is a cardinal precursor of congestive heart failure (CHF). The Framingham data has confirmed the causal role of hypertension in the pathogenesis of CHF. Analysis of this data has revealed a two to three fold risk of development of CHF in patients with hypertension which persists after correction for confounding factors. There is also a clear relationship between the height of the blood pressure and the incidence of cardiac failure. Further support is provided by that fact that all major hypertension trials have shown a significant reduction in the incidence of CHF with treatment.[29]

Abnormalities of both systolic and diastolic function have been demonstrated both in experimental animal models and in humans with LVH. It is now clear that, in the early stages of hypertension, the problem is one of diastolic dysfunction, This is the consequence of both the hypertension and LVH. Angiotensin II has been shown to have direct effects on diastole. Stimulation of the angiotensin II receptors leads to abnormalities in calcium handling and impairment of active relaxation.[30] Furthermore stimulation of cardiac fibroblasts and subsequent interstitial fibrosis leads to abnormalities in passive relaxation.[31,32]

Systolic functional abnormalities appear to occur at a later stage in the patient with LVH, and although these follow the diastolic dysfunction, it seems more likely that the processes underlying diastolic and systolic dysfunction are independent. The exact contribution of cardiac dysfunction to the increased mortality in patients with hypertensive LVH remains to be determined.

Ultrastructural changes in the myocardium

Microscopic examination of the myocardium of patients with hypertensive LVH reveals both qualitative and quantitative changes. In addition to the myocyte hypertrophy, there is an intense interstitial fibrosis. The fibrosis occurs both as a reparative fibrosis following myocyte necrosis and also as reactive fibrosis which begins as a perivascular fibrosis and extends in the interstitial space.[33] The accumulation of this fibrous tissue results in distortion of tissue structure leading to an increase in

ventricular stiffness and ultimately the development of diastolic dysfunction. It has also been implicated as a substrate for ventricular arrhythmias.[34] Mechanisms responsible for the accumulation of fibrous tissue can be conveniently grouped into three groups:

- Hormonally mediated coronary vascular hyperpermeability.
  Experimental work has demonstrated that elevated plasma angiotensin II levels lead to abnormal coronary vascular hyperpermeability also shown to be independent of the associated venoconstriction and hypertension.[35] This demonstrated hyperpermeability leads to macromolecules entering the interstitial space which in turn stimulate cardiac fibroblast proliferation and subsequent collagen synthesis.
- Direct neurohormonal stimulation of collagen synthesis. The cardiac fibroblast has cell surface receptors for angiotensin II, endothelins and aldosterone. Stimulation of these receptors leads to an increment in the synthesis of collagen in a concentration-dependent manner.[36]
- Intracellular autocrine and paracrine signalling.
  Changes in the extracellular matrix (ECM) in hypertension have attracted considerable interest, in part fuelled by the discovery of biochemical markers of interstitial fibrosis which has allowed non-invasive monitoring of the process. The extracellular matrix is a dynamic structure with simultaneous synthesis and removal of matrix components. The major collagens synthesized are type I and III, both of which are secreted by the cardiac fibroblast in pro-collagen form with an aminoterminal and carboxyterminal peptide respectively.[37] These terminal peptides are cleaved in the extracellular space allowing integration of the collagen helix into the growing fibril. Elevated levels of procollagen type III aminoterminal peptide (PIIIP) and procollagen type I carboxyterminal peptide have been shown in hypertension and appear to reflect ongoing fibrosis.[38]

Matrix metalloproteinases (MMP), a family of zinc and calcium dependent endopeptidases, play a key role in the degradation of collagen. MMPs have very potent proteolytic activity which is controlled in a major part by the production of specific naturally occurring inhibitors called tissue inhibitors of matrix metalloproteinases (TIMPS) (Fig. 2.2).[39] An elevation in TIMP levels would thus lead to the accumulation of collagen through inhibition of degradation. Published studies have now documented an elevation in TIMP-1 in untreated patients with essential hypertension reflecting a role for inhibition of the degradation of collagen in the process of fibrosis.[40,41]

Factors controlling the development and progression of LVH

Clearly hypertension plays an important role in the development and progression of LVH, and its mechanical effects on the left ventricle have been shown to be a potent stimulus to the development of hypertrophy. Mechanical stretch of the heart can lead to acceleration of protein synthesis and activation of a number of important intracellular signals that contribute to cardiac hypertrophy.[42,43] In addition, stretching of the heart muscle appears to influence gene activity, which then leads to encoding of growth factors and the development of hypertrophy.[44] Evidence continues to

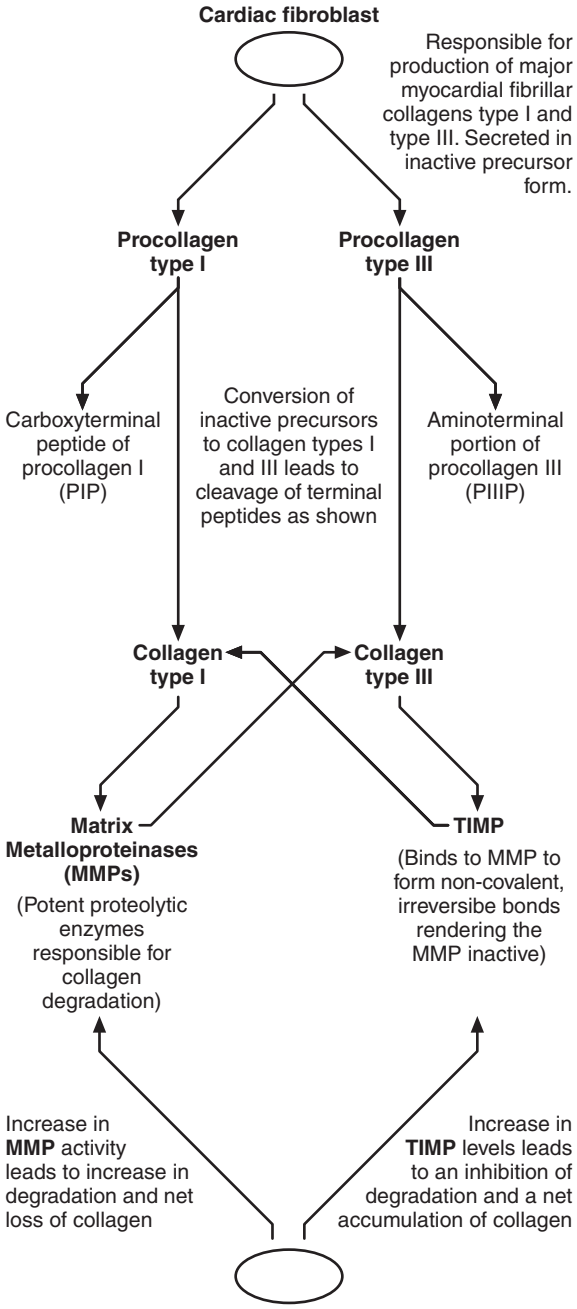

Figure 2.2
Regulation of collagen turnover.

accumulate regarding the importance of cell biology in our understanding of the development of LVH.

Despite the importance of hypertension in the development of LVH, the correlation between the magnitude of the hypertrophy and office BP readings is less than might be expected, although this correlation improves when using 24 hour ambulatory BP monitoring (ABPM). The value of ABPM is well established in confirming the diagnosis of hypertension and in estimating the efficacy of antihypertensive treatment.

However recent work has shown additional benefits of 24 hour BP monitoring. Firstly, cross-sectional studies have shown that target organ damage relates more closely to average 24 hour BP, than office BP readings.[45–47] Secondly, follow-up studies have shown that cardiovascular morbidity and target organ deterioration correlate more closely with ambulatory BP readings than with office readings.[47] Finally, recent evidence from the SAMPLE study confirms that the degree of LVH is more closely reflected by 24 hour average BP and also shows that a treatment-induced reduction in LVH is accounted for more by a reduction in 24 hour BP than office readings.[48] Although there appears to be clinical importance in 24 hour ABPM the correlation with the extent of LVH is still rather disappointing. This underscores the influence of other factors that influence the development of LVH.

The renin angiotensin aldosterone system

Components of the renin angiotensin aldosterone system appear to have an intrinsic role in the pathogenesis of hypertension. Angioten-

sinogen (AGT) acts as a substrate for renin and appears to be the rate-limiting step in the production of angiotensin I. In humans polymorphisms of this gene have been linked to hypertension although this relationship does not seem to persist throughout ethnic groups.[49] There are both indirect and direct actions of angiotensin II on the heart. The indirect cardiovascular actions of angiotensin II involve the central nervous system (stimulation of thirst and increased sympathetic outflow), stimulation of aldosterone synthesis and release which has been shown to be important in the development of both myocyte hypertrophy and myocardial fibrosis, the maintenance of vascular tone and increased heart rate secondary to enhanced sympathetic activity.[50] The direct cardiac actions of angiotensin II include stimulation of cardiac contractility, elevation of protein synthesis and activation of the membrane phospholipase.

Angiotensin II is one of the most potent pressor substances known and it has many additional roles important in the pathogenesis of hypertension. Angiotensin II has potent inotropic effects mediated by its action on calcium homeostasis and transmembrane conductance. In addition it has a role as a growth factor and has been shown to increase the expression of proto-oncogenes which are involved in the regulation of cell proliferation. Vascular effects of angiotensin II have also been documented. Short-term effects consist of direct contraction of arterioles and facilitation of sympathetic nervous transmission whilst long-term effects are mediated by its mitogenic properties on smooth muscle cells and cardiac fibroblasts. Classically the renin angiotensin system has been viewed systemically with its effector hormones being generated in the circulation. However several reports have demonstrated renin-like activity in extrarenal tissues and expression analysis of renin, AGT, and converting enzyme has shown that they are co-expressed in several tissues.[51] This has provided the basis for the theory of de-novo tissue synthesis. It is possible that locally produced angiotensin II would influence local sodium handling, vascular tone, cardiac contractility and mass. Thus the effect of the renin angiotensin system on the development of LVH should be viewed not only on a systemic basis but also as a locally active system.

There are a number of examples, both experimentally and clinically, of the contribution of angiotensin II towards the development of cardiac hypertrophy. Models of cardiac hypertrophy by pressure loading have revealed an increase expression of ACE mRNA thought to lead to an increment in the generation of angiotensin II in this setting.[52,53] The attenuation of LVH in this model following the administration of an ACE inhibitor added further evidence confirming the central role of the renin angiotensin system in the development of LVH.[54]

Further studies revealed that chronic infusion of angiotensin II into rats caused an increase in LV mass that occurred even when the pressor activity of the peptide was blocked.[55] Subpressor doses of angiotensin II are also known to increase left ventricular to body weight ratio and doses of an ACE inhibitor not causing BP reduction have been shown to prevent the development of left ventricular hypertrophy.[50] However, it should be remembered that the beneficial effects of an ACE inhibitor are not purely due to blockade of the production of angiotensin II. Indeed the inhibition of the degradation of bradykinin appears to play a central role in the efficacy of ACE inhibitors. Studies have shown the

importance of bradykinin in the antihypertensive effect of ACE inhibitors[56] and the antihypertrophic effects of ACE inhibitor infusions are offset by the addition of a bradykinin antagonist. This would suggest that regression of LVH by ACE inhibitors may be in part due to accumulation of bradykinin.[57] Some doubt however, has been expressed about this theory. Experimental work has shown that endothelial cells are required in culture to allow bradykinin to express its antihypertrophic effects, suggesting that bradykinins effects are endothelial-dependent.[58] Since hypertension is associated with a degree of endothelial dysfunction, this casts doubt on the relative importance of bradykinin in the regression of LVH.

Despite the weight of evidence demonstrating the importance of the renin angiotensin system in the development of LVH it is important to remember the multifactorial nature of hypertension and LVH. This was elegantly demonstrated by experiments using an AT-1 knockout mouse model which reveal that this genetic manipulation was not sufficient to prevent the development of LVH.[59]

The adrenergic nervous system

Adrenaline infusion into dogs results in significant myocardial hypertrophy that is independent of changes in blood pressure.[60] In addition, the alpha-adrenergic agonist norepinephrine increases total RNA and RNA:DNA ratio. In contrast, blockade of alpha and beta-receptors can prevent norepinephrine-induced increases in LV mass.[61] There is good evidence that the beta receptor agonist isoprenalin, can also cause an increase in myocyte volume.[62] The situation is complicated because it also results in necrosis, making difficult the interpretation of the cardiac weight change. At a cellular level it is known that beta-adrenergic receptor stimulation causes an increase in c-AMP, and this precedes other events such as cell growth leading to LVH.

Other factors

It is beyond the scope of this chapter to detail all of the other factors that are important in the development and progression of LVH. These include the additional growth factors, such as insulin, thyroid hormone and growth hormone, and other factors such as age, race, gender, weight, heredity and co-existing cardiovascular disease. These factors should be borne in mind when considering both the development and regression of hypertrophy (Fig. 2.3).

Regression of LVH

The conclusion from all the information to date is that a reduction in LV mass will follow

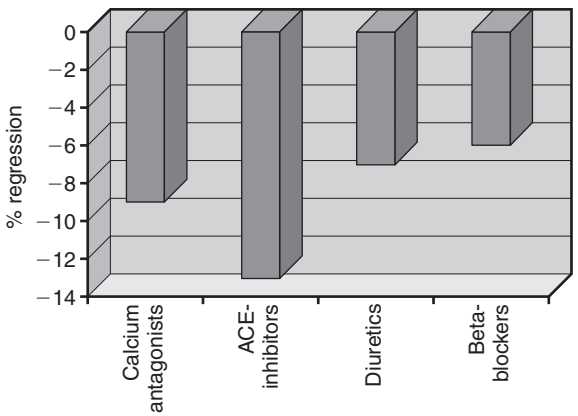

Figure 2.3
Adapted from Schmeider et al.[65]

appropriate blood pressure reductions with most classes of antihypertensive medication. The exception to this is the directly acting vasodilators. Non-pharmacological measures, such as weight loss and dietary sodium reduction have been shown to be effective in lowering blood pressure coupled with a decrease in LV mass and in addition to pharmacologic therapy.

Methods available to assess regression of LVH remain flawed. Experimental animal work has the benefit of allowing direct measurement of LV mass while clinical studies rely on indirect measurement. Echocardiographic measurement which is available, is superior to the ECG and carries no risk to the patient. It has a number of drawbacks, as noted previously, which should be borne in mind when assessing the data available. Nonetheless, clinical trials have confirmed earlier studies indicating that regression of LV hypertrophy does occur.[63] It is not possible, of course, to say whether this regression means a reversal towards normality since baseline LV mass is seldom known. The meta-analyses, with all their shortcomings, have also confirmed reductions in left ventricular mass in association with reduction in blood pressure.[10,64,65] Thus it is now established that regression does occur.

Optimal BP level

It remains unclear what the optimal BP level is for LVH regression. Concerns have been expressed about the presence of a J-shaped curve and that vigorous lowering of BP may lead to an excess of cardiovascular events. It is on the background of this debate that the Hypertension Optimal Treatment (HOT) study set out to assess the optimum target diastolic BP.[66] Patients were enrolled and allocated to a target diastolic BP of <90 mmHg, <85 mmHg or <80 mmHg. Treatment was with the calcium antagonist Felodipine with the addition of ACE-inhibitors and beta-blockers if necessary. Systolic BP was lowered on average by twenty-eight mmHg and diastolic by twenty-two mmHg. This is striking when compared to reductions reported in previous meta-analyses of nine–ten mmHg in systolic pressures and of five–six mmHg in diastolic pressures.

The results demonstrated that there was beneficial effects in lowering BP to 140/85 mmHg. Further reduction to 120/70 mmHg was shown to be safe although, this appeared to give little additional benefit. Active lowering of BP was particularly efficacious in the subgroup with diabetes mellitus. Overall the reduction in cardiovascular event rate was considerably more impressive than in previous prospective trials probably reflecting the pronounced lowering of BP. In addition the HOT study showed a 12% regression of LVH, with a regime based on a long-acting dihydropyridine. This group of drugs had not previously been shown to consistently regress LVH. The aggressive BP lowering in the HOT study may well have been a factor in its regression.

Antihypertensive drugs

A major stimulus for the identification of possible differential effects of antihypertensive agents on regression of LVH was provided by the work of the late Dr RC Tarazi and his colleagues from the Cleveland Clinic. Their landmark published in 1977 showed that in spontaneously hypertensive rats methyldopa and hydralazine reduced BP to the same degree. Yet only methyldopa caused regression of LVH.[67] One possible explanation for this

difference was the contrasting effects of the drugs on the renin-angiotensin and adrenergic nervous system. Subsequent studies have confirmed the view that vasodilator drugs, which provoke a reflex increase in heart rate, appear to be less effective in causing regression of LVH, whereas drugs which inhibit the adrenergic or renin-angiotensin system are generally more effective. One obvious advantage of these experimental animal studies was that the heart could actually be weighed and studied pathologically. These options were clearly not available in the clinical arena.

At around this time, the advent of echocardiography provided the clinician with a non-invasive cardiac investigation of considerable potential for measuring LV mass and wall thickness and for serial measurements in patients on different antihypertensive agents. Although earlier studies with ECG measurements had shown improvement with control of BP, it was difficult to determine whether this was due to changes in LV mass or to other factors known to influence ECG voltages. However, with echocardiography (whereby left ventricular wall thickness can be measured and LV mass can be derived) more accurate interpretation became possible; but it has to be borne in mind that a number of the early echo studies were undertaken before a validation of the echo derived LV mass was complete. In addition, these early studies were often poorly designed: they contained an inadequate number of patients many of whom did not have significant LVH and many of whom were often receiving multiple drug therapies. It was often difficult to draw any meaningful conclusions from these studies. The quality of later trials improved substantially, although it remains difficult to conduct an ideal trial in terms of study design. For example, cross-over trials are not possible because LV mass does not return to its pre-treatment level at the same rate as the BP. In fact it may take the BP several months to return to its pre-treatment level. This is further complicated by ethical considerations about allowing LVH to recur in patients in whom regression has been achieved. It follows, therefore, that the entry of a patient into a trial who has previously had antihypertensive therapy may compromise the analysis, as the patient's ventricle may have already undergone an unknown amount of regression. Additionally, as discussed, there remain the inherent drawbacks of serial measurements of LVH.

In response to this lack of clear and informative data, the prerequisites for an acceptable study of LVH regression have been established.[68] Studies should be randomized, double-blind and use a validated measure of LV mass. The comparative group should be placebo or one or more active agents. From 250 to 300 patients should be enrolled per treatment arm and followed up for a minimum of 6 months. The study population should be ethnically diverse and contain a significant proportion of patients with baseline LVH. This study may allow accurate direct comparisons of the efficacy of individual agents. However studies to determine the prognostic benefits of regression of LVH would require up to 600 patients in each treatment arm with a 4-year follow up.

Published studies and meta-analyses have tried to address these issues but not always successfully. The 1997 veterans study was the first large study to compare the effects on echocardiographically determined LV mass of single agent antihypertensive therapy in a large group of ethnically diverse patients with definite hypertension and a high prevalence of

LVH (45%) at study entry.[69] This study used monotherapy with the prototypes of the six major classes of antihypertensive therapy. The two major findings are, firstly, that short-term therapy with antihypertensive agents (8 weeks) has no effect on LV mass and, secondly, after one year of treatment the greatest reductions in LV mass were achieved by Captopril (−15 g) and hydrochlorothiazide (−14 g) with a minimal reduction with atenolol (−4 g). The remaining antihypertensive agents (clonidine, prazosin, and diltiazem) showed no significant effect. It should be noted the lack of female patients, the high drop-out rate and problems with follow-up echocardiograms limit the validity of this study.

The meta-analyses by Dahlof et al[10] and Cruickshank et al[64] concluded that LVH regression was best achieved by ACE inhibitors. Dahlof's data revealed a 16% reduction with ACE inhibitors, an 11% reduction with diuretic therapy, a 9% reduction with calcium channel blockade and an 8.5% reduction with beta-blockade. Cruikshank's data confirmed ACE inhibitors as the most potent agents and also confirmed the importance of duration of treatment and the magnitude of BP reduction.

The most meaningful meta-analysis is that presented by Schmieder et al[65] who included only randomized studies comparing two or more treatments with blinded echo assessment of LV mass. A reflection of the deficiencies in the available data was that out of 471 reviewed studies only 39 met the above criteria with only 13 having placebo controlled groups. The data was in keeping with previous analyses and confirmed that regression of LVH was greater with active drug rather than placebo. In addition, the regression was determined by the pretreatment LV mass, the blood pressure control and the duration of therapy. Analyses of the difference between agents was adjusted for the above variables. ACE inhibitors again showed the greatest fall in LVM (13.3%), followed by calcium channel blockers at 9.3%, diuretics at 6.8% and beta-blockers at 5.5% (Fig. 2.4).

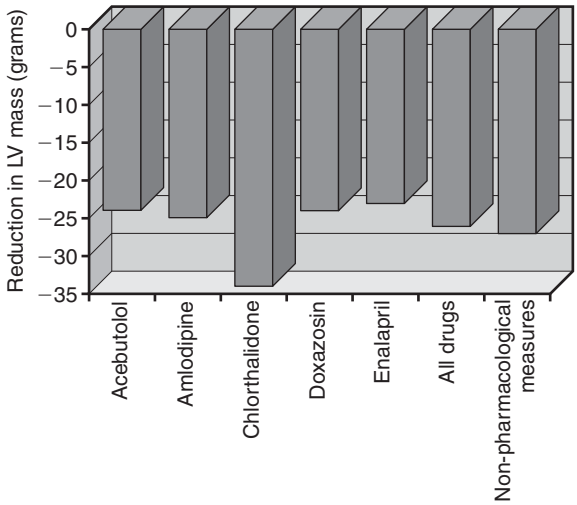

Figure 2.4
TOHMS study. From Neaton et al.[71]

Despite the shortcomings of meta-analyses it can be concluded from these studies that the reduction in LV mass is influenced by pretreatment LV mass, duration of drug treatment and the class of drug used. However it should be emphasized that the most important determinant of LVH regression is appropriate BP reduction.

Non-pharmacological measures

The degree of LVH for any given BP is dependent on a myriad of variables. These include BP level, degree of obesity, degree of

BP lability, age, sodium intake, neurohormonal and intracellular factors. Thus with this thinking in mind there has been considerable interest in the investigation of non-pharmacological measures to reduce BP and LV mass. These have concentrated on weight loss, sodium restriction, exercise and reduction in alcohol intake.

McMahon et al conducted a randomized controlled trial in young obese hypertensive patients.[70] The patients were randomized to placebo, weight reduction or metoprolol therapy. The group allocated to purely weight reduction lost an average of 8.3 kg which resulted in a reduction of systolic pressure of 14 mmHg and diastolic of 13 mmHg. There was a resultant reduction of 20% in LV mass. The reduction in blood pressure and LV mass was significantly greater in the weight loss group than either the placebo or metoprolol group.

The TOMHS study used a 'placebo' group which received nutritional-hygienic advice to reduce weight, dietary sodium intake, alcohol intake and to increase physical activity.[71] The combination of these measures resulted in significant reduction in BP and LV mass. Comparison between non-pharmacological measures and the five chosen pharmacological therapies revealed no significant difference between regression of LVH with the exception of the diuretic group (Fig. 2.5). The effect of sodium restriction on regression of LVH has also been studied compared to placebo in patients with mild-moderate hypertension.[72] This study revealed a reduction in systolic BP of 9 mmHg, in diastolic BP of 6.5 mmHg and in the LV mass of 5.4%. This was coupled with a minimal weight reduction of 2 kg. In summary these results confirm the efficacy of non-pharmacological treatment in hypertension and in the subsequent regression of LVH. Non-pharmacological measures should be an integral part of any treatment regime aimed at regression of LVH.

Diuretic therapy

Diuretic therapy has once again been recommended by JNC VI as one of the first line antihypertensive agents.[73] This is based on a wealth of data on its efficacy and safety. However the use of diuretics in hypertension remains disappointingly low, partly because of concerns about hypokalemia the possible adverse effects on lipid and glucose metabolism and their apparent lack of efficacy in reducing LVM in hypertension.[73]

However three recent studies have shown diuretic therapy to be effective and safe in the reduction of LVM in hypertension: TOMHS, SHEP and the Veterans study.

The TOMHS study was a comparison of five antihypertensive monotherapies with non-

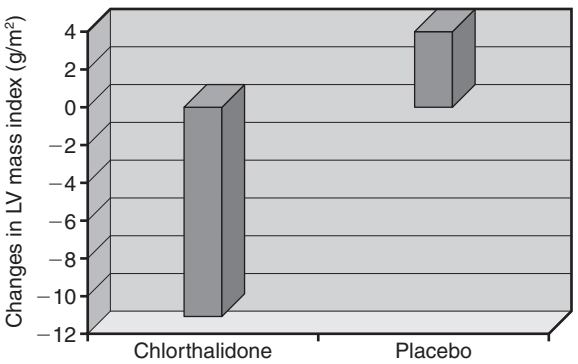

Figure 2.5
SHEP study. From the Systolic Hypertension in the Elderly Program Co-operative Research Group.[74]

pharmacological means of lowering BP.[71] This study showed Chlorthalidone to be the only agent to show a significant reduction in left ventricular mass versus non-pharmacological treatment at one year follow-up. There was a non-significant difference between the active treatments with regard to regression. Chlorthalidone reduced LV mass by 34 g versus 24–27 g in other treatment strategies. In addition those participants who received chlorthalidone as a second agent showed a further reduction in LV mass suggesting an independent effect of chlorthalidone on the reduction in LVM mass. The obvious criticism of this study is the inclusion of only 13.6% of patients with LVH, thus limiting the power to show differences between therapies.

The SHEP study enrolled an elderly cohort with isolated systolic hypertension comparing diuretic therapy with placebo.[74] The diuretic arm showed a significant reduction in LVM vs placebo after a three year follow up. This reduction in LV mass appeared to be due to an actual decrease in wall thickness (Fig. 2.6).

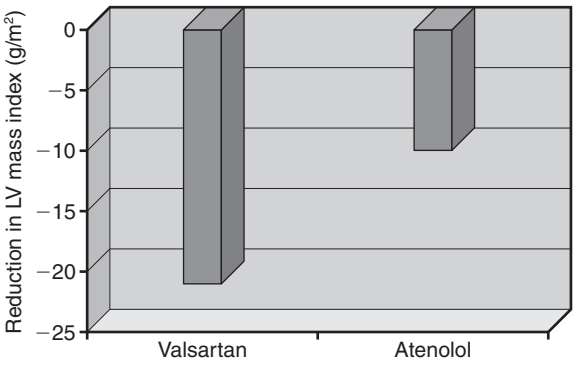

Figure 2.6
Valsartan vs Atenolol. Adapted from Thurman et al.[93]

Finally, a study comparing six antihypertensive agents in a group of veterans with mild-moderate hypertension again demonstrated the ability of thiazide diuretics to reduce LV mass.[69] Moreover this reduction in LVM was not associated with any adverse metabolic consequences. Thus recent evidence would suggest that diuretic therapy is a cheap, safe and effective antihypertensive treatment strategy which contributes towards regression of LVH.

Calcium antagonists

There has been considerable recent controversy surrounding the use of calcium antagonists in hypertension. Several studies have suggested adverse cardiovascular consequences of the use of dihydropyridines. The most quoted is the meta-analysis by Furberg which shows an apparent increase in cardiovascular deaths in patients treated with short acting Nifedipine.[75] There was a clear dose response relationship with the highest mortality in the group on 80 mg per day. Pahor et al studied prospectively elderly patients with hypertension.[76] This revealed a relative risk of 1.7 for all cause mortality in the group treated with Nifedipine, which was significant when compared with other treatment groups.

The data appears to be particularly concerning in patients with type II diabetes with the ABCD,[77] FACET[78] and MIDAS trials[79] all reporting less favourable outcomes with the use of dihydropyridine calcium antagonists. However the HOT trial showed encouraging results with the use of Felodipine in patients within the main cohort who had type II diabetes.[66]

Concerning reduction in LV mass, there are again mixed results. Dihydropyridines have

been extensively studied and the TOMHS study showed amlodipine to have a similar profile of BP reduction and moderate regression of LVH.[71] However Papademetriou et al showed that despite equivalent reduction in BP, six months of therapy with hydrochlorothiazide was associated with a substantial reduction in LV mass, significantly greater than the medium-acting dihydropyridine Isradipine.[80]

One elegant study compared verapamil with atenolol in an elderly cohort of patients.[81] The study involved studies of left ventricular function at rest and with exertion. The authors also had a period of treatment withdrawal allowing blood pressure levels to return to pretreatment values. Both drugs had similar antihypertensive effects and yet only verapamil therapy resulted in an appreciable reduction in LV mass. Additionally verapamil was shown to improve diastolic dysfunction.

The main published meta-analyses show calcium antagonists to be effective in the regression of LVH. Most studies report a reduction in LV mass of around 9% with treatment and the HOT study shows LV regression of 12% which is comparable with other agents with the exception of ACE inhibitors. What should be concluded from all this controversy is a difficult question. In summary, current evidence is consistent with an association between regression of LVH and calcium channel blockers.

Beta-blockers

Beta-blockers have been shown in large placebo controlled prospective trials to be effective in the reduction of cerebrovascular and cardiovascular morbidity and mortality. However the picture of regression of LVH with beta blockers, again, is a mixed one. The TOHMS study indicated a similar reduction in LV mass to that of most other antihypertensives.[71] In addition meta-analyses have demonstrated a reduction of 5.5–8.5% in LV mass associated with beta-blocker use.[10,64,82] However, as noted above, a direct comparison between beta-blockade and verapamil revealed beta-blockers to be ineffective in regression of LVH despite a reduction in blood pressure.[81]

In a further study, metoprolol was added to felodipine and compared to felodipine alone in a double-blind parallel group study.[83] The addition of metoprolol did not appear to cause any difference in the degree of regression of LVH. Furthermore, in a 6-month comparative trial between the ACE inhibitor ramipril and atenolol, atenolol resulted in only a 6 g/m^2 reduction whilst ramipril produced a reduction of 19 g/m^2.[84]

An explanation for these apparently contradictory results is that beta-blockers appear to cause a reduction in ventricular wall thickness but may increase left ventricular cavity dimensions, thus offsetting any favourable effect on calculated LV mass.

ACE inhibitors

As discussed earlier the renin angiotensin system plays a central role in the development of LVH. Angiotensin II has been shown to stimulate various growth factors, cytokines, fibroblast activity which leads to interstitial fibrosis and myocyte hypertrophy. It is thus perhaps not surprising that the evidence demonstrating regression of LV hypertrophy with ACE inhibitors is the most convincing of any antihypertensive agent in both placebo-controlled and comparative studies.[78,85–87] The 1997 Veterans Study which compared six anti-

hypertensive agents reported that ACE inhibitor therapy resulted in the largest comparative fall in LV mass (15 g).[69] In addition, the three most complete meta-analyses have confirmed ACE inhibitors as the most potent agents with regards to regression of LVH.[10,64,65] This appears to be a class effect. ACE inhibitors also have the most convincing animal evidence of the ability to regress the interstitial fibrosis that occurs in hypertensive heart disease.[88,89] This suggests that ACE inhibitors result in the most favourable qualitative as well as quantitative regression of LVH.

Angiotensin II antagonists (AT1RA)

AT1RA are a relatively recent addition to the armoury of antihypertensive agents with an attractive side-effect profile. A possible advantage the AT1RAs have over ACE inhibitors is that they block non-ACE-dependent angiotensin II generation which occurs within the myocardium and, evidence, now suggests in the vasculature.[90] Another beneficial effect may be the supra-normal angiotensin II levels and the resultant unopposed stimulation of the AT2 receptor. The AT2 receptor, once thought to be of little functional importance, appears to have important functional roles. Research suggests that stimulation of this receptor results in antiproliferative, and apoptotic effects in addition to the generation of nitric oxide.[91,92] However, a potential disadvantage of AT1RA therapy is that it excludes the beneficial effects of bradykinin which, as discussed earlier, may play a supporting role in the antihypertrophic effect of the ACE inhibitors.

The trial evidence with regards to the ability of AT1RA to regress LVH is as yet limited. A double-blind study of atenolol versus valsartan amongst untreated hypertensives with LVH showed a significant reduction in LV mass index with Valsartan (21 g/m^2) which was greater than that observed with atenolol (10 g/m^2)[93] (Fig. 2.7). Tedesco et al compared the effect of losartan and hydrochlorothiazide in a group of 87 patients with essential hypertension in a randomized study.[94] Losartan therapy was shown to result in significant regression of LVH after 10 months follow-up. Furthermore, Kahan et al demonstrated the effectiveness of Irbesartan in the reduction of LVH in a comparative study with atenolol.[95] These studies were in contrast to the previous negative studies by Cheung et al[96] and Himmelman et al[97] which both failed to show an antihypertrophic effect of AT1RA. It should however be remembered that both these studies were small with limited follow-up.

The current role for AT1RA until further data is available would seem to be reserved for patients intolerant of standard agents or in resistant hypertension. However perhaps the future may be in the combination of AT1RA and ACE inhibitors.

Alpha-blockers

The ALLHAT study is a randomized, double-blind, active controlled trial that compares representative agents from 4 classes of antihypertensives (chlorthalidone, doxazosin, amlodipine and lisinopril) to determine whether any meaningful differences exist.[98] After interim analysis the treatment arm which involved doxazosin was discontinued by the safety monitoring board.[99] Patients receiving doxazosin had a statistically significant 25% increase in the risk of combined cardiovascu-

lar disease events including double the risk of development of cardiac failure. Full discussion of this study and the implications of this finding are beyond the scope of this chapter. However the result challenge the widely held assumption that the most important parameter in the treatment of hypertension is BP reduction and not the antihypertensive drug used.

Neutral endopeptidase inhibitors

Preliminary evidence is now available on omapatrilat which is a combined neutral endopeptidase inhibitor and an ACE inhibitor. Animal studies reveal potent antihypertensive action and target organ protection.[100,101] No data is as yet available on long-term use in man or long-term safety. However this will undoubtedly be the source of ongoing research.

The importance of regression of LVH

It has been assumed that, since the presence of LVH confers an increased risk of cardiovascular morbidity and mortality, then regression of this hypertrophy and the reversal of the structural changes would result in an improved prognosis for the patient. However as yet we do not have any definite evidence that regression of LVH translates into lives saved of hypertensive patients. There is some evidence from observational studies using serial ECG assessment of LVH (Framingham data)[102] and an Eastern European retrospective study[103] which show that regression of LVH confers prognostic benefits. However these studies are far from definitive.

If we look at surrogate endpoints, then the picture is more encouraging. There is good evidence that regression of LVH results in maintenance of systolic function and improvement in diastolic dysfunction. This has been shown with a variety of antihypertensive agents and following the discontinuation of therapy to remove the influence of BP reduction and the drugs themselves.[81,104,105] It is recognized that myocardial ischaemia plays a central role in the adverse cardiovascular risk associated with hypertension. Thus it is important to analyse the effects of regression of LVH on the presence of myocardial ischaemia. Studies in animal models and humans have shown evidence of a reduction in myocardial ischaemia coupled with a reduction in LV mass.[106,107]

Ventricular arrhythmias constitute a further surrogate endpoint for regression of LVH where, again, studies have shown a reduction in ventricular ectopy with a reduction in LV mass.[108]

The qualitative assessment of what constituents of the myocardium which regress has been emphasized in this chapter. Various methods of the assessment of myocardial fibrosis are currently being evaluated. The technique with the greatest potential is undoubtedly the measurement of biochemical markers of fibrosis and this is now being used by a number of groups. There is currently emerging information which points to differences in the ability of antihypertensive drugs to alter the fibrous content of the myocardium[89] and this is an area which clearly merits further study, particularly in regard to its relationship to alterations in LV function.

Conclusion

Left ventricular hypertrophy is a potent and independent risk factor for cardiovascular mor-

bidity and mortality. There is now clear evidence that regression of LVH occurs following adequate BP control with most antihypertensive agents. Well designed comparative assessment of the effects of the main antihypertensive agents are limited. However, after reviewing the available evidence it appears that ACE inhibitors are currently the most effective group in the regression of LVH and there is also experimental evidence to suggest that this group of drugs is also the most effective in regression of interstitial fibrosis.

However it is important to emphasize that the key factor in regression of LVH is BP reduction with other factors such as duration of therapy, pretreatment LV mass and agent used playing less important roles. It has been shown that to achieve appropriate BP control in the majority of patients additional antihypertensive agents will be required. Thus, ultimately small differences in the ability to regress LVH in a clinical setting may be of minor significance when compared with the overall goal of appropriate BP control.

Available evidence reveals that regression of LVH facilitates a maintenance of normal systolic/diastolic function, a reduction in myocardial ischemia, a maintenance of normal cardiac structure and a reduction in ventricular arrhythmias. However, the main question which persists unanswered is whether regression of hypertensive LVH translates into a prognostic benefit over and above the degree of blood pressure lowering. Ongoing prospective long term morbidity and mortality studies, such as ALLHAT[98] and LIFE[109] are likely to resolve some of these issues.

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3

Cholesterol and Coronary Heart Disease: the Current Status

Chris J Packard

Introduction

Recent clinical trials have proven beyond doubt the benefit of cholesterol-lowering with statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) in both primary and secondary prevention and have changed medical practice worldwide.

The following chapter explores how these drugs decrease by 25–45% the risk of a first or recurrent myocardial infarction (MI), lower cardiovascular mortality and improve overall survival. Since the magnitude of the relative risk reduction on statin therapy appears not to be modified by lipid phenotype, age, sex or concomitant risk factors, all may benefit potentially from treatment. This leaves physicians and health authorities in a dilemma as to who to treat, and strategies need to be developed to direct drug use to those who will benefit most. The second part of the chapter discusses current thinking on treatment algorithms in primary and secondary CHD prevention. Emphasis is placed on absolute risk of a coronary event as the best guide for targeted drug use.

Current concepts of the role of lipids in atherosclerosis

Plasma lipid transport

Epidemiological surveys in the 1960s and 1970s identified a number of major risk factors for the development of coronary heart disease (CHD), namely raised blood pressure, smoking and raised serum cholesterol levels. Cholesterol in the MRFIT study[1] was shown to have a strong, graded but curvilinear relationship with CHD incidence. The gradient of the association of cholesterol with risk was steep above a value of 6.5 mmol/l (250 mg/dl), moderate in the range 5.2–6.5 mmol/l (200–250 mg/dl) and relatively shallow below 5.2 mmol/l (200 mg/dl) (Fig. 3.1). It was the changing nature of this curve that gave rise to different action thresholds in early guidelines written in the late 1980s[2] and suggested more aggressive treatment at higher cholesterol levels. The present review will focus on cholesterol management in cardiovascular disease, however, it should not be forgotten that the genesis of atherosclerosis is multifactorial and lipid control is but one avenue open to the physician to reduce CHD risk in patients. Best results will be obtained by diligent attention to all factors.

In considering the role of cholesterol in

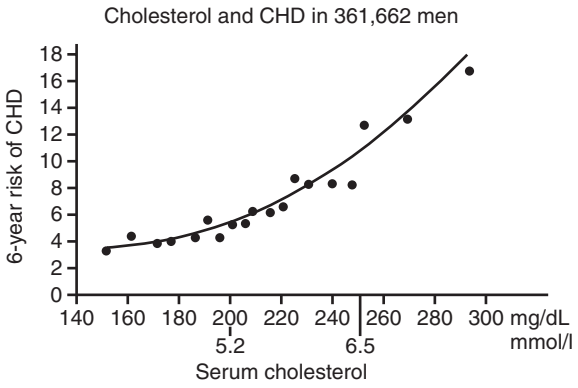

Figure 3.1
Relationship between serum cholesterol and CHD risk. Reproduced with permission from Martin et al 1986.[1]

concepts, atherosclerosis is the result of this superabundance of lipid.

LDL is the major cholesterol-carrying plasma constituent and it is believed to contribute most to the deposition of cholesterol in both growing and complicated atherosclerotic lesions. Originally it was thought to vary little in structure from person to person, being basically a complex of apolipoprotein B and cholesteryl ester solubilized in a micellar phospholipid 'droplet'. However, it is now recognized that the lipoprotein comprises a number of subfractions that differ in size, density and, importantly, atherogenic potential (Fig. 3.2). Individuals with a high propor-

atherosclerosis and coronary disease it is important to remember that the lipid is insoluble in the aqueous medium of plasma and is transported in the form of lipoproteins. The fate of these large particulate plasma constituents (Fig. 3.2) is determined largely by the proteins on their surface. Hence, particles that contain apolipoprotein B (chylomicrons, very low-, intermediate- and low-density lipoproteins VLDL, IDL, LDL) generally carry cholesterol into tissues, those in which the major protein is apoA (i.e. high density lipoproteins (HDL)) function to transport cholesterol from tissues sites back to the liver for excretion or re-utilization. The lipid transport system is geared to work at low plasma concentrations, i.e. LDL cholesterol levels of about 3.0 mmol/l as seen in healthy young adults.[3] Dietary imprudence, obesity and genetic factors contribute to generating an excess of lipoproteins in the circulation and according to current

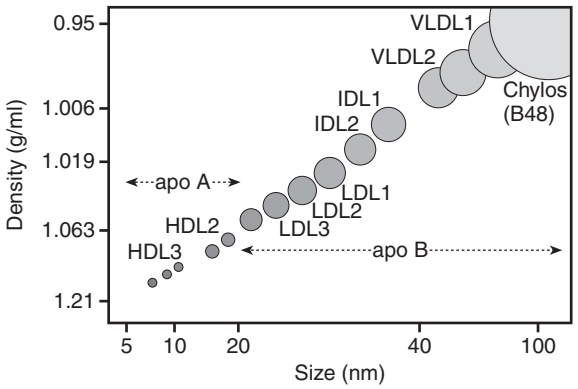

Figure 3.2
Plasma lipoprotein spectrum. The common classes of lipoproteins are displayed, together with their approximate size and density. Axis scales are arbitrary, but particle diameters are to scale relative to one another. Important subdivisions are shown for VLDL, IDL, LDL and HDL. A description of apoB-containing lipoprotein subfractions is given in Packard and Shepherd 1997[8] *and Krauss 1998.*[9]

tion of small, dense LDL (LDL-3) exhibit a 3–7 fold increased risk of CHD.[4,5] This heightened atherogenicity has been linked to the finding that smaller LDL penetrate the artery wall more readily than their larger counterparts, are more likely to bind avidly to arterial wall proteoglycans[6] and are more readily oxidized. Usually, when the LDL subfraction distribution shows a preponderance of small particles there is an associated increase in plasma triglyceride and a reduction in HDL cholesterol levels. This syndrome is now recognized as a discrete dyslipidemia and has been termed the atherogenic lipoprotein phenotype.[7] Models have been published suggesting that the changes in LDL structures and HDL concentration are secondary to the elevation in plasma triglycerides.[8,9]

Also elevated in hypertriglyceridemia are populations of lipoprotein particles termed 'remnants'. These are the cholesterol-enriched products of the lipolysis of chylomicrons and VLDL. Though a minor contributor to total plasma cholesterol, these species are believed to be highly atherogenic as they are the only naturally occurring lipoproteins that cause unregulated cholesterol deposition in macrophages, cells which are involved in the initiation of atherosclerosis.[9]

Unstable plaques

Classically, atherogenesis and the events that led to an acute coronary episode such as MI or sudden death were understood in terms of a 'linear' paradigm. That is, as plasma LDL levels increased so did the accretion of cholesterol in the artery wall. Macrophages and smooth muscle cells moved to areas of substantial LDL deposition and there became resident and died, so contributing to an ever growing lesion that eventually gave rise to symptoms when it became large enough to occlude the artery. Seminal work from Davies[10] and Falk et al[11] in recent years has shown this paradigm to be incorrect. Their critical observation was that the lesions most likely to give rise to clinical events were not the largest (i.e. >70% stenotic) but were moderate-sized plaques (25–50% stenotic) that may appear unremarkable on a coronary angiogram or indeed not appear to encroach into the lumen at all. These smaller plaques were the ones most likely to rupture (i.e. were 'unstable') provoking a thrombotic episode that led to vessel occlusion whereas larger lesions which may cause symptoms of stable angina were unlikely to suffer a break in the lesion cap or erosion of the endothelial surface (Fig. 3.3).

A great deal of work has gone into the investigation of determinants of stable vs unstable plaques.[10] The former are relatively rich in smooth muscle cells and collagen (which acts as stabilizing extracellular matrix) and poor in cholesterol while the latter have a high content of macrophages, T-lymphocytes and are cholesterol-rich. Plaque rupture is now thought to be the key step in the initiation of an acute coronary event. It is envisaged that 'activated' lymphocytes and macrophages in the cap of the plaque (Fig. 3.3) release cytokines that promote smooth muscle cell death, possibly by apoptosis and also secrete metalloproteinases that degrade collagen and other matrix components.[11,12] The weakened cap breaks and exposes the elements of the blood to the pro-thrombotic subendothelial space. A thrombus forms which, if contained within the artery wall, leads to quantum plaque growth. However, if the clot formed is large, possibly because of high circulating

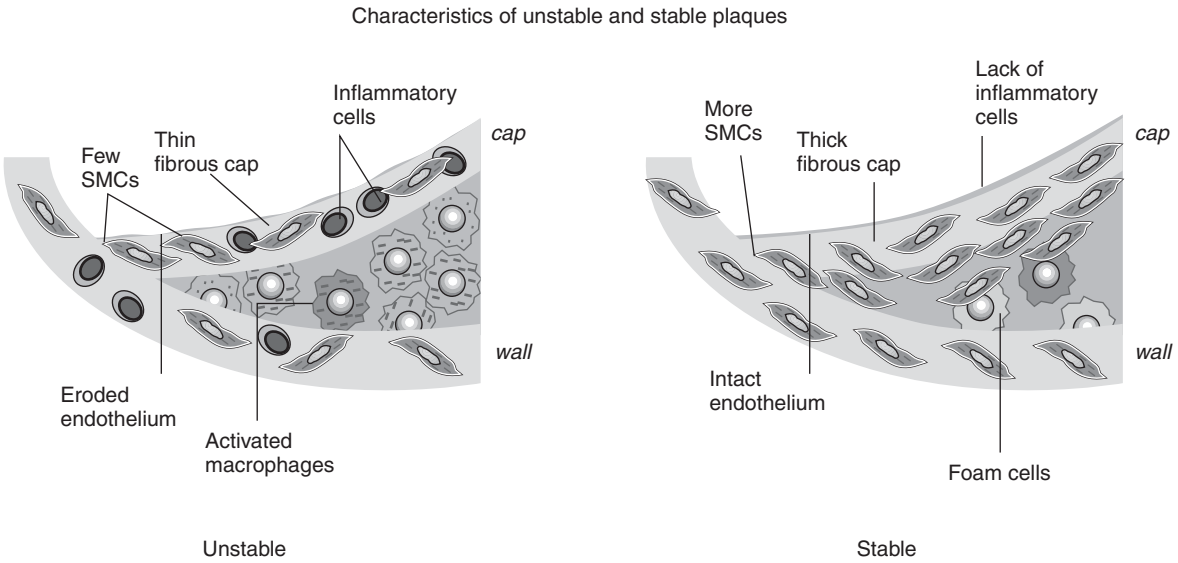

Figure 3.3
Stable and unstable atherosclerotic plaques. This schematic shows the shoulder region of a plaque where it joins the artery wall. Stable plaques have a high content of smooth muscle cells and collagen with few macrophages. Unstable plaques are enriched in macrophages with less collagen and smooth muscle cells.

concentrations of haemostatic factors then occlusion of the artery leads to ischemia and an episode of unstable angina, MI or death. Erosion of the surface of the plaque can also give rise to thrombus formation. It is recognized increasingly that chronic inflammation is a likely cause of plaque cap instability. Several major epidemiological surveys have demonstrated that plasma markers of inflammation such as C-reactive protein and interleukin-6 are elevated in those at high risk of an acute coronary event.[13,14]

The outcome of lipid-lowering (or other intervention) trials must be understood in light of this new thinking on the cause of MI. Plaque size is no longer the central feature that determines prognosis, a finding which helps to explain why very small changes in lumen diameter in coronary angiographic studies were associated with substantial reductions in risk of a coronary event.[15] Indeed, it is quite conceivable that benefit follows an increase in plaque size as smooth muscle cells repopulate the cap of the plaque, divide and grow and secrete collagen to stabilize the structure. The new paradigm has implications for the interpretation of angiographic-based trials and ultimately for the management of patients. Interventions which trade advantageous lipid changes against an increase in thrombosis may produce no net benefit as exemplified by the recently published HERS trial.[16] Likewise, using angioplasty to

relieve symptoms at the expense of plaque rupture may not provide the desired long-term benefit.[17]

Outcome studies using lipid lowering agents

Pre-statin era trials

Following the formulation of the 'cholesterol hypothesis' (based on epidemiological studies) that cholesterol-lowering would give rise to a reduction in CHD events, three large-scale primary prevention studies were launched. The first and, to date, largest trial was the WHO clofibrate study which showed a modest effect of therapy on reducing risk of MI (non-fatal MI fell 25% on clofibrate) but raised issues of long-term safety since death rates in the drug-treated group exceeded those in the placebo.[18] The Lipid Research Clinics (LRC) trial, conducted in the USA, randomized 3806 asymptomatic, hypercholesterolemic men to placebo or cholestyramine treatment.[19] The drug was more efficacious than clofibrate in reducing LDL cholesterol but compliance was poor and overall the LDL reduction in the active treatment group was only 12.6% compared to placebo. This was associated with a 19% reduction in risk of fatal plus non-fatal MI and commensurate decreases in the incidence of positive exercise tests, angina and coronary bypass surgery. Relating LDL reduction to risk reduction, the LRC investigators found evidence to suggest that for every 1% LDL decrease there was a 2% drop in CHD risk.[20] Gemfibrozil was employed in the Helsinki Heart Study (HHS)[21] to test the possibility that lowering plasma triglyceride and raising HDL cholesterol could provide benefit in addition to any LDL change. The principal finding of this study was a 34% decrease in the combined endpoint of fatal plus non-fatal MI. This risk reduction was attributed in part to the LDL fall on gemfibrozil but also to the HDL increase.[22] The greatest effect of the drug (about a 70% risk reduction) was seen in a subgroup of patients who at baseline had moderately elevated serum triglyceride levels and a high LDL/HDL ratio.[22]

For some physicians the evidence of these early studies was sufficient to embark upon lipid-lowering treatment as a major strategy for coronary prevention and consensus guidelines were generated that were taken up to various degrees in different countries. Others cited the lack of data for a benefit of lipid lowering on cardiovascular death and total mortality and were wary of widespread use of lipid-lowering drugs.[23,24] It was only with the publication of landmark statin-based trials that the 'cholesterol hypothesis' was regarded as finally proven and that cholesterol control became a major method of coronary disease prevention for both the specialist and general physician.

Primary Prevention Trials

Two large scale statin-based primary prevention trials were published in the 1990s. The West of Scotland Coronary Prevention Study (WOSCOPS) in 1995[25] and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) in 1998.[26] WOSCOPS was a trial of pravastatin therapy at a single dose of 40 mg/day in 6595 men aged 45–64 years who were moderately hypercholesterolaemic but had not had a MI (Table 3.1). The 6605 recruits to AFCAPS were men and women, age 45–73 years who had no signs or symptoms of ischemic arterial disease

	WOSCOPS	*AFCAPS/TexCAPS*
Subjects	6595 men	5608 men/997 women
Mean age	55 years	58 years
Smokers	44%	12%
Hypertensives	16%	22%
Mean baseline values		
Plasma triglyceride (mmol/l)	1.70	1.80
LDL cholesterol (mmol/l)	5.00	3.90
HDL cholesterol (mmol/l)	1.14	0.94
Primary endpoint	Non-fatal MI/CHD death	Non-fatal MI/CHD death/Unstable angina
Reduction in primary endpoint	31%	37%
Reduction in CABG/PTCA	37%	33%
Reduction in CV mortality	32%	29% (NS)
Reduction in total mortality	22%	−3.4% (NS)

Data reproduced from Shepherd et al 1995[25] and Downs et al 1998.[26]

Table 3.1
Major statin trials: primary prevention.

and had average plasma cholesterol but low HDL; here lovastatin (20–40 mg/d) was used and titrated to achieve specific lipid goals. Both trials gave very similar results in terms of risk reduction and advanced greatly understanding of the potential benefits of statin therapy in CHD prevention in asymptomatic patients across a broad range of plasma lipid levels and coronary risk.

WOSCOPS

Pravastatin lowered LDL cholesterol by 26% (from a mean of 5.0 to 3.7 mmol/l), reduced plasma triglyceride by 12% and increased HDL 5%. Over the 5 years of the study therapy was associated with a 31% risk reduction in the combined primary endpoint of definite fatal + non-fatal MI (from an absolute of 7.9%/5 yr to 5.5%/5 yr), a 37% decrease in the requirement for revascularization (absolute risk for placebo of 2.5% compared to 1.7% on pravastatin) and for the first time a significant reduction in cardiovascular mortality of 32% (Table 3.1). Given the controversy over the potential detrimental effects of cholesterol-lowering drugs it was important to find that the non-cardiovascular death rate was unaffected by drug (11% decrease, $p = 0.54$) and that all-cause mortality was reduced 22% ($p = 0.051$ by log rank test, $p = 0.037$

adjusted for baseline risk factors[27]). As in any primary prevention trial there was a substantial drop-out over the years of the study so that after 5 years about 30% of subjects were no longer on active treatment. Withdrawal rates were identical for the two treatment arms and adjustment for non-compliance increased the relative risk reduction of the primary endpoint and cardiovascular mortality to 37–38% while relative risk of revascularization was decreased 46%.[28] Thus, substantial benefits were obtained by the use of pravastatin treatment against a background of no observable detriment in terms of either major or minor side effects. Furthermore, the risk reduction on treatment began early with a lower CHD incidence on pravastatin evident after about 6 months.[25] This is to be compared with a lag period of 2–3 years before risk reduction was observed in earlier trials.[19,21] One interpretation of this finding is that statin therapy is more effective than other forms of lipid lowering at plaque stabilization which is now thought to be the main mechanism of benefit (as opposed to plaque size reduction).

Sub-group analysis in WOSCOPS revealed that risk reduction was largely independent of patient status: older and younger subjects, smokers and non-smokers and those with some signs or symptoms of atherosclerotic disease versus those who were asymptomatic, all experienced a similar benefit from treatment.[25] This led to the important conclusion that the individuals who gain most from statin treatment are those at the highest absolute risk since they will enjoy the greatest absolute risk reduction.[29] In contrast to the findings in the gemfibrozil-based HHS, the effect of pravastatin on CHD incidence did not differ by baseline lipid phenotype,[30] again supporting the concept of a uniform relative risk reduction.

AFCAPS/TexCAPS

Possibly the most extraordinary feature of the AFCAPS trial is the low risk of the patients recruited (Table 3.1). Subjects were drawn from a healthy, middle-aged/older population of men and women whose major risk factor was a below average HDL. The primary endpoint as in WOSCOPS included fatal plus non-fatal MI but also unstable angina which is also recognized increasingly as a manifestation of 'acute coronary syndrome' generated by plaque rupture.[11,12] Stable angina on the other hand is linked more to the presence of flow-limiting, large (>70% stenotic) lesions.[10] LDL levels were reduced 26% by lovastatin with, as for WOSCOPS, small changes in plasma triglyceride and HDL cholesterol.[26] Relative risk reduction for the primary endpoint was 37% (absolute risk 5.45%/5 yr on placebo compared to 3.4%/5 yr on lovastatin) and for fatal plus non-fatal MI (equivalent to WOSCOPS primary endpoint) was 40% (2.8%/5 yr on placebo vs 1.65%/5 yr on drug). Revascularizations were more frequent than in WOSCOPS reflecting differing clinical practice in the two countries, and again significantly reduced by therapy (4.65%/5 yr on placebo vs 3.1%/5 yr on lovastatin). The cumulative event-curves showed an early drug benefit with lovastatin-treated subjects having a lower incidence of events from about 6 months.[26] New episodes of unstable angina (which was carefully documented in this study) were reduced by treatment, supporting its common pathogenesis with MI and its susceptibility to lipid lowering. No significant differences were observed in safety parameters between the two treatment groups. However, mortality from all causes was too low to draw any firm conclusions about long-term effects (Table 3.1). The major conclusion from

AFCAPS and WOSCOPS is that in primary prevention all are likely to benefit from statin therapy, not just hypercholesterolaemics or subjects with a specific lifestyle or risk factors. This result carries important consequences for coronary prevention strategies as outlined below. It moves the issues from the medical realm into an economic and social one.

Secondary Prevention Trials

The importance of risk factor modification in general and lipid lowering in particular has been accepted for primary prevention for a long time but it is only recently that epidemiological data became available to show the strong association between cholesterol levels and risk of a recurrent MI.[31] These observations led to the formulation of trials to test the cholesterol hypothesis in secondary prevention and a number of landmark studies have now been completed which show dramatic benefits of statin therapy. So convincing are the findings across a wide range of cholesterol levels that cholesterol lowering using statins is now accepted clinical practice in patients with established CHD.

4S

Published in 1994, the Scandinavian Simvastatin Survival Study[32] was a watershed in our appreciation of the size of the benefit available from statin-based cholesterol lowering and an exemplar of how to obtain incontrovertible evidence from a clinical trial. Focused firmly at the design stage on proving a reduction in cardiovascular and total mortality, the findings of the study changed almost overnight many cardiologists' views on lipid lowering. Patients across a wide range of plasma cholesterol, 5.5–8.0 mmol/l, were randomized to simvastatin (20–40 mg/day) or placebo if they had a previous MI or unstable angina (Table 3.2). Follow-up was continued until a pre-specified number of deaths (10% of the 4444 cohort) occurred. LDL cholesterol was decreased 35% by active therapy and this was associated with 42% reduction in coronary death and a 30% decrease in overall mortality ($p = 0.0003$ for the latter, the significance values are a tribute to good trial design). Major coronary events occurred in 22.6% of the placebo group and 15.9% of the simvastatin groups over the 5.4 years of follow-up (a risk reduction of 33% in an endpoint similar to that used in WOSCOPS and AFCAPS). The relative risk reduction in 4S was again not influenced by sex, age or other patient characteristics and was additional to any benefit attendant on antihypertensive treatment.[32] There were a substantial number of non-cardiovascular deaths and adverse events (cancers etc.) and these were equal in the two treatment arms of the study.

Recent publications from 4S have revealed that simvastatin therapy prevents the appearance of less severe manifestations of atherosclerosis such as intermittent claudication, carotid bruit, new and worsening angina and stroke.[33]

CARE

Most patients who experience a MI have unremarkable plasma cholesterol levels, near to the average seen in the general population. The rationale behind the Cholesterol And the Recurrent Events (CARE) study[34] was to ask if lipid lowering was of benefit in these individuals as it is in hypercholesterolaemic patients (Table 3.2). 4159 patients who had a MI were recruited in centres in the USA and Canada and randomized to receive 40 mg/day

	4S	*CARE*	*LIPID*
Subjects	3617 men/ 827 women	3583 men/ 576 women	7498 men/ 1516 women
Mean age	59 years	59 years	62 years
Smokers	26%	21%	10%
Hypertensives	26%	43%	41%
Angina only	21%	0%	36%
Prior CABG/PTCA	8%	54%	41%
Aspirin	37%	83%	82%
Plasma triglyceride (mmol/l)	1.5	1.8	1.6
LDL cholesterol (mmol/l)	4.9	3.6	3.9
HDL cholesterol (mmol/l)	1.2	1.0	0.9
Primary endpoint	Total mortality	CHD death plus non-fatal MI	CHD death
Reduction in MI/CHD death	31%	24%	24%
Reduction in CABG/PTCA	37%	26%	20%
Reduction in CV mortality	42%	20% (NS)	24%
Reduction in stroke	24% (NS)	31%	19%
Reduction in total mortality	30%	18% (NS)	22%

Data reproduced from The Scandinavian Simvastatin Survival Group 1994,[32] Pedersen et al 1998[33] and Sacks et al 1996.[34]

Table 3.2
Major statin trials: secondary prevention.

pravastatin or placebo. On entry plasma cholesterol had to be below 240 mg/dl (6.2 mmol/l) with the result that mean baseline LDL cholesterol was only 139 mg/dl (3.6 mmol/l). The majority of patients were on aspirin, and antihypertensive medication and over half had undergone a revascularization procedure. Thus, the drug had to generate clinical benefit in addition to the best care available at the time. LDL was lowered 32% by pravastatin with a 14% fall in plasma triglyceride and a 5% rise in HDL. Active treatment reduced the risk of the primary endpoint (CHD death plus non-fatal MI) by 25% from an absolute risk of 13.2%/5 yr on placebo to 10.0%/5 yr on pravastatin. Repeat revascularization occurred in 18.8% of the placebo group but only 14.1% of the treated group (27% risk reduction). In this study stroke was a pre-specified outcome and

pravastatin treatment produced a 31% ($p < 0.03$) reduction in this endpoint. Clinical benefit was as great in women as in men, and in the over 60s as in younger subjects.[34] Diabetics (15% of the cohort) also showed a significant risk reduction.[35] CARE was the first trial to investigate the benefits of lipid lowering in the lower range of the LDL distribution in the population. One of the more controversial findings in the study was the apparent lack of a clinical effect of the drug in subjects whose LDL cholesterol was <125 mg/dl (3.2 mmol/l) at baseline despite the presence of a LDL reduction.[34] This phenomenon has been explored further by the CARE investigators who have suggested that a threshold exists below which LDL reduction generates no commensurate CHD risk reduction.[36] There is support for this postulate from WOSCOPS[30] although 4S found a less obvious attenuation of benefit with greater LDL reductions.[37]

LIPID

LIPID (Long-term Intervention with Pravastatin in Ischemic Disease) is the largest of the statin studies.[38] Conducted in Australia and New Zealand, it randomized 9014 men and women post-MI or with unstable angina to receive placebo or pravastatin (40 mg/day). There was a wide range of plasma cholesterol (4.0–7.0 mmol/l) on entry and treatment with pravastatin gave highly significant risk reductions of 24% in CHD death and 23% in total mortality. In LIPID as in CARE, stroke was a stated outcome measure and was reduced 20% by pravastatin therapy (Table 3.2). Because of the large cohort and substantial number of events, this trial offers useful information on less frequent major and minor adverse events. In particular, the imbalance in breast cancer seen in the CARE trial (with more cases on pravastatin[34]) was not confirmed in LIPID where the incidence was equal in the placebo and pravastatin groups.[38]

Recent fibrate trials

With the establishment of statin treatment as a pillar of coronary prevention, attention has turned to new aspects of lipid regulation, particularly the potential benefits of increasing HDL cholesterol. The trials described above all report that HDL is one of the most powerful determinants of risk, even in subjects treated with statins.[30,36,37]

Conceptually, there is as much to be gained from raising HDL 20% as lowering LDL by the same amount[30] and since these are independent risk factors, the benefits are likely to be additive.

VA-HIT

The Helsinki Heart Study provided a clear indication that fibrate treatment which elevates HDL cholesterol was associated with reduced risk of CHD in primary prevention. The Veterans Administration-HDL Intervention Trial (VA-HIT)[39] gave even more convincing evidence of benefit of this approach in secondary prevention. This study randomized 2531 men with established coronary disease and low HDL cholesterol (1.0 mmol) and low or average LDL levels (<3.6 mmol/l), gemfibrozil (1200 mg/day) or placebo for a period of 5 years. The drug raised HDL cholesterol 6%, lowered triglyceride 31%, but had no significant effect on LDL. A 22% ($P < 0.001$) risk reduction was seen in the primary end point of non-fatal MI/CHD death on gemfibrozil and similar benefits were observed for stroke and hospitalization for congestive heart failure.

BIP

The Bezafibrate Infarction Prevention (BIP) Study[40] was less convincing than VA-HIT. Despite having more recruits and a larger mean increase in HDL cholesterol (18%) there was no significant difference between drug and placebo in coronary event rates. Only the subgroup with high baseline triglycerides on entry exhibited a significant benefit of bezafibrate treatment (reminiscent of the Helsinki findings).

Lipid lowering in coronary prevention

The main area of concern in lipid lowering has moved from a question of whether to treat to a question of who to treat. Figure 3.4 depicts the 'pyramid' of evidence now available to support the application of aggressive LDL lowering, specifically with statins to coronary prevention. The drugs employed (lovastatin, pravastatin, simvastatin) have been shown to be individually highly effective in reducing virtually all manifestations of coronary disease and for pravastatin, cerebrovascular disease as

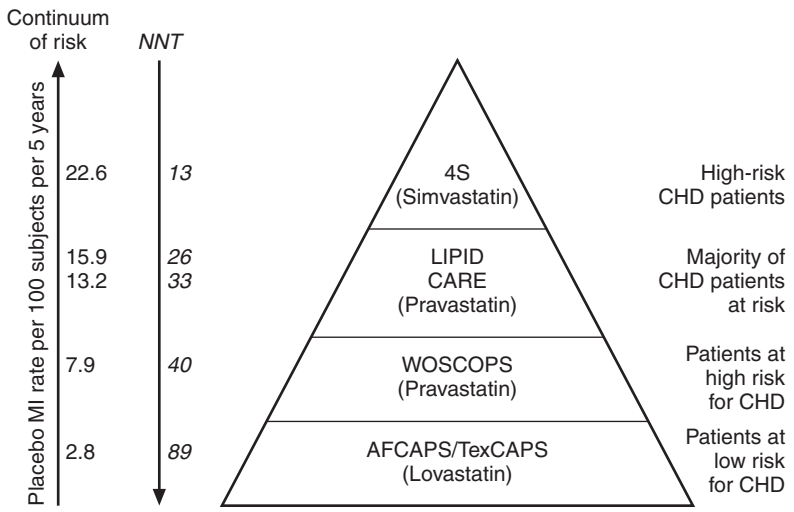

Figure 3.4

'Pyramid' of statin trials. The five major statin-based outcome trials are ranked according to the risk of the placebo groups. Rates of a coronary event are given for each study. The pyramid shape denotes the fact that the fraction of the general population to which the trial results could be applied increases substantially from 4S through to AFCAPS. Number needed to treat (NNT) to prevent one coronary event is given for each risk category. This is the reciprocal of the absolute risk reduction in each trial (i.e. placebo group absolute risk minus active treatment group absolute risk over 5 years).

well. A constant finding in the major trials is a uniform relative risk reduction on treatment irrespective of the lipid phenotype or concomitant risk factors present in the recipient including age and sex. The absolute benefit is, therefore, proportional to the absolute risk of the subject considered for treatment. A scale of absolute risk of MI is given in the figure to illustrate the 10-fold range seen in the population. The absolute risk reduction can be used to calculate the 'number needed to treat (NNT)' to prevent a clinical event (NNT = reciprocal of reduction in absolute risk). This is a useful rule of thumb to compare different therapeutic approaches independent of cost. Cost is important, of course, where medication is expensive and formal cost-effectiveness analyses have been performed for both WOSCOPS[41] and 4S.[42] On the basis of the findings cogent arguments have been advanced to show that for both primary and secondary prevention the cost/benefit ratio falls into the range considered acceptable by many health purchasing authorities. However as NNT increases, which it does dramatically for subjects at low risk, then so does the proportion of the population that falls into the treatment net with consequences for pharmacy budgets (even if statins were reduced in price), laboratory testing and physician/nurse time. Further, the impact of medicalizing a significant portion of the population must be considered if all sections of the community represented by the pyramid were considered candidates for drug treatment. The following discussion as to who to treat is based on the recognition that at present only a minority of the population should be directed towards statin treatment and these individuals should be identified on the basis of their absolute risk of a coronary event.

Secondary prevention

Evidence for the clinical benefit of statins in prevention of recurrent coronary events is compelling and a simple, defensible strategy is to prescribe the drugs for all who have had a MI, regardless of the cholesterol level (i.e. without assessing it!). However, a more thoughtful but still robust approach is probably needed to ensure that all who need statin treatment receive it and also that lifestyle measures designed to reduce risk are given appropriate emphasis. At the moment, many post-MI, post-CABG patients who merit statin therapy do not get it because they 'fall through the cracks' in the division of responsibility between cardiologists, cardiac surgeons and general practitioners.

Elements of a possible secondary prevention strategy are presented in Fig. 3.5. Identification of appropriate patients is straightforward because individuals present with symptoms of CHD. Further, these are a well-defined minority of the population, the processing of which will not place a strain on hospital or GP resources and for whom the return in clinical benefit is very high. The trials described above indicate that men and women who manifest disease should be treated equally. Certainly, in studies such as CARE there was no sex difference in the incidence of recurrent coronary events.[34] It is true that women generally (particularly before menopause) are at a much reduced risk compared to men but those who express disease proceed with a similar clinical course to their male counterparts. Secondary prevention should not be restricted to the post-MI situation since patients with less severe manifestations of the 'acute coronary syndrome' have also been shown to benefit, i.e., post-CABG, post-angioplasty and those

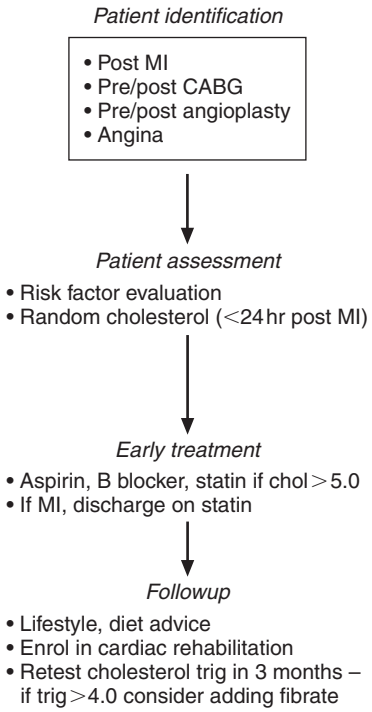

Figure 3.5
An approach to secondary prevention based on early assessment and rapid treatment with statins. Adapted from Wood et al 1998.[46]

with unstable angina.[32,38] Indeed risk of a coronary event in such groups is so high that they can be placed comfortably in the secondary prevention category (Figs 3.4, 3.5). Evaluation of patients should be as speedy as possible. Subjects admitted to hospital with a MI can have a reliable assessment of plasma cholesterol made within 24 hours of onset of the event – the test could be added to the admission laboratory profile. Those on waiting lists for revascularization should have cholesterol levels determined as part of the routine clinic visit. In all instances it is important that lipid levels are not viewed in isolation but that other risk-reducing manoeuvres are implemented concurrently, e.g. stopping smoking, low-dose aspirin treatment, blood pressure control.

Initiation of treatment

A statin can be started on the basis of the initial cholesterol level (which need not be fasting). In light of the CARE findings it is wise at the moment to consider a lower limit of about 5.0 mmol/l (equivalent to a LDL of 3.0 mmol/l) as a threshold below which statin treatment may not deliver the desired benefit. However, the vast majority of patients are above this level and could be started on treatment early, possibly prior to discharge for MI survivors. This helps prevent follow-up failures.

Diet and lifestyle

Cholesterol lowering diets are effective, producing a 5–10% reduction in LDL but this is not considered aggressive enough treatment in secondary prevention and so drugs are usually required. Diet has its place, though, for other reasons. Consumption of antioxidants in vegetables and fruit (such as vitamin E) has been shown to be effective in reducing risk post-MI[43] as has a high intake of fatty fish.[44] Therefore, dietary and lifestyle advice (smoking cessation, adoption of regular exercise) is of central importance in secondary as well as primary prevention but in the former it is introduced concurrently with drug therapy.

Fibrates

Given the results of the CARE and VA-HIT trials – studies that were performed on similar

populations (mainly men with average cholesterol level) in the USA, it may be worth suggesting that in patients with established coronary disease and LDL levels below 3.1 mmol/l (120 mg/dl), a fibrate be considered as adjunct therapy if the HDL is below 1.0 mmol/l. It is accepted that the effect of statin–fibrate combinations on outcome is not yet clear but current data from clinical trials indicate a potentially highly favourable impact on CHD. Concerns have been expressed over the prescription of such drug combinations but more recent experience suggests that they can be used safely.[45]

Goals of therapy

Goals of lipid-lowering therapy are still under discussion. The revised guideline of the European expert committee is a target LDL cholesterol of 3.0 mmol/l[46] and that of the revised NCEP (US National Cholesterol Education Panel) is 100 mg/dl (2.6 mmol/l).[47] Clinical trials have provided evidence for a law of diminishing returns with respect to LDL lowering once LDL cholesterol falls about 25% or below a value of about 3.2 mmol/l (125 mg/dl).[30,36,37] Thus, a LDL target of 3.0 mmol/l[46] accompanied by a LDL reduction in the order of 25% seems to be appropriate given our current state of knowledge. If plasma triglyceride is high on statin and HDL low then as noted above, consideration could be given to adding a fibrate to the regimen. This will help correct the hypertriglyceridemia, raise the HDL and shift the LDL size profile towards a less atherogenic state[48] even if further falls in the level of LDL are modest.

Choice of statin is a current issue since there are a number on the market world-wide (atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin). They vary in cost, the extent of LDL lowering and the amount of evidence available to support their long-term safety and efficacy. Preference should be given to the drugs that have been tested in large scale secondary prevention trials (pravastatin and simvastatin at present).

Primary prevention

Around one-third to one-half of patients who suffer an MI do not survive to enjoy the benefits of secondary prevention. Thus, any coronary prevention strategy must incorporate an approach to primary prevention that is feasible, affordable and likely to produce the greatest benefit for the effort involved. A possible approach is given in Fig. 3.6. Of key concern is the determination of absolute risk in an asymptomatic subject since this is inversely associated with NNT (Fig. 3.4) and hence resource utilization. Individuals with signs or symptoms of CHD such as claudicants or those with minor ECG abnormalities who do not fall into the secondary prevention category are also considered as high risk.[27,29] The reluctance of many physicians and health authorities to embark upon a primary prevention programme is founded on the potentially open-ended nature of the problem, in contrast to well-defined secondary prevention. Identification of those at-risk by simple methods helps resolve the issue and setting a risk threshold for follow-up provides a manageable number of subjects to process.

Evaluation

Risk assessment can be conveniently performed using either charts or computer-based algorithms based on the findings of the Framingham[49] or PROCAM[50] epidemiological

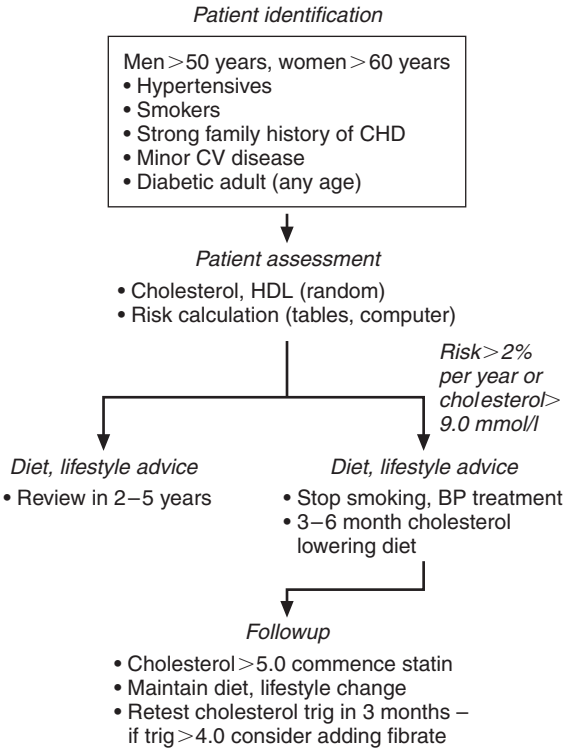

Figure 3.6
A 'high risk' primary prevention program. This program selects people for risk assessment according to age and other factors likely to predispose to a risk of a coronary event of >2% per annum if the cholesterol level is elevated. Lipid threshold and goals are based on the European guidelines. Adapted from Wood et al 1998.[46]

surveys. These take into account the multifactorial nature of CHD and permit estimation of the global absolute risk of a coronary event over a given period, e.g. 10 years. Thresholds for detailed assessment and follow-up can then be set in knowledge of the NNT figure and an approximation as to the fraction of the population that would harbour such a risk level. European guidelines[46] indicate that a risk of coronary event of >2% per annum identifies high-risk subjects who require treatment. UK government guidelines set the threshold at 3%.[51] If the European level is applied to the WOSCOPS population then about 40% of these men had a >2% per year risk; they experienced a 31% risk reduction and so the NNT was in the acceptable range even for hard-pressed physicians.

Goals of therapy

Dietary change and lifestyle advice are the cornerstone of a primary prevention strategy and should be given a reasonable period in which to work (Fig. 3.6). If the plasma cholesterol, which should be tested along with HDL (a random specimen will suffice for both assays) at the initial risk assessment, fails to fall below 5.0 mmol/l over a 3–6 month diet trial then statin is started with the objective of reducing the cholesterol to <5.0 mmol/l (LDL cholesterol <3.0 mmol/l). Again, the findings from clinical trials indicate that a LDL reduction of about 25% is sufficient to provide optimum benefit and the law of diminishing returns operates again.[30] Note that in the European guidelines the target for LDL is the same in primary and secondary prevention whereas NCEP suggests 130 mg/dl (3.4 mmol/l) as the goal in primary prevention.[47]

In choosing which statin to employ it should be noted that only lovastatin and pravastatin have been tested in primary prevention. However, the atherosclerotic process is believed not to differ in high-risk subjects with and without manifest disease and so simvastatin can be added as a third alternative because of the long-term safety data available from 4S.

Future prospects for coronary prevention

Coronary prevention has been transformed by the availability of statin therapy that has proved to be safe and efficacious in long-term clinical trials. The cholesterol hypothesis is now accepted dogma and it appears as though clinical benefit from lipid lowering comes not from regression of atherosclerotic lesions but from stabilization of fragile, moderate-sized plaques. The precise details of how statins help prevent plaque rupture is as yet unclear (Fig. 3.7). Reduction in LDL is certain to play a major role since in the oxidized form this lipoprotein is known to promote endothelial damage and activation of macrophages. The removal of other atherogenic lipoproteins from the circulation (IDL, chylomicron and VLDL remnants) following receptor activation is also likely to contribute to reducing the cholesterol content of macrophages and smooth muscle cells in lesions. However, because statins inhibit a basic metabolic pathway which produces not only cholesterol but also important molecules such as geranyl and farnesyl derivatives that have roles in cell growth, the possibility exists that the drugs may have direct effects on the cells of the plaque. Evidence for such an action is emerging from clinical trial data[30,52] and biochemical experiments.[53] For example, in CARE a pro-inflammatory state as evidenced by elevated plasma C-reactive protein levels was associated with a 2-fold increase in CHD risk but this risk component was attenuated markedly by pravastatin treatment, apparently outside of any lipid changes generated by the drug.[52] While all statins reduce LDL by a similar mechanism, their pleiotropic effect vary markedly according to their molecular structures.[53] Thus, if these actions turn out to contribute substantially to the overall risk reduction then the drugs may not generate equal clinical benefit for a given cholesterol decrease.

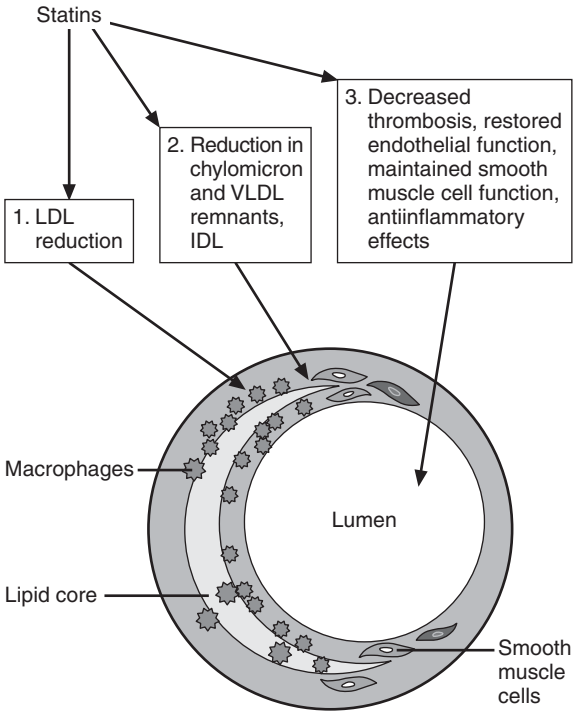

Figure 3.7
Potential mechanisms of action of statins. The early and large risk reductions seen in statin trials may derive from multiple actions of the drugs. LDL reduction is a central component but did not explain all of the benefit observed, for example, in WOSCOPS.[30] By stimulating receptor activity in the liver, statins will promote clearance of other atherogenic apoB-containing lipoproteins from the circulation. The drugs also exhibit potentially beneficial effects through apparently lipid-independent mechanisms as reviewed by Rosenson and Tangney 1998.[53]

Stroke reduction appears to be an added benefit of statin therapy as seen in the CARE and LIPID studies (Table 3.2).[54,55] This is despite the lack of an epidemiological relationship between cholesterol level and risk of stroke. Current thinking is that ischemic stroke has a similar pathogenesis to the atherosclerosis, thrombosis-based acute coronary syndrome and therefore risk of a cerebrovascular event is diminished by plaque stabilization. It should be noted that stroke prevention with statins has only been shown to occur in subjects who have had a MI and may be viewed as an additional reason for early and aggressive therapy in secondary prevention. Further trials are needed to test if these drugs can prevent stroke in the general population.

Gaps in our knowledge exist with respect to the generalizibility of the trials described here which were conducted largely in middle-aged Caucasian males. What are the benefits of primary prevention in women and the elderly (>75 years)? Do the risk reductions seen in the major studies translate across ethnic groups such as Asians and African–Americans where there are known differences in the epidemiology of CHD.[56] These questions are the subject of further active research in this area.

Acknowledgements

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4

Hormone Replacement Therapy and Cardiovascular Disease: Are the Cardiovascular Benefits Established?

Graham Jackson

Introduction

Over recent years, coronary artery disease (CAD) in women has become a topic of increasing interest and its importance as the major cause of morbidity and mortality in women has now been realized.[1,2] Whilst CAD in pathologic terms respects no race, religion or gender, it does present in different clinical ways and with different degrees of severity depending on gender and race. These differences in presentation are clinically important because they affect how CAD is detected and diagnosed as well as managed. It is not just the clinical and pathologic aspects of CAD which should be the focus of attention, but also the psychologic and social impact of CAD on the family unit, whether the sufferer be male or female. Beneath the wealth of statistics and guidelines – some of which are discussed in this chapter – there is an individual who needs personalized care. Whilst statistics may guide the care of patients, patients themselves should never be treated as statistics.

Epidemiology

The Framingham study, which began in 1948, is the major epidemiologic source of information on CAD in both men and women.[3] As a generalization, the clinical presentation of CAD in women occurs 10 years later than in men: the age of 50 years appears to be the point when the incidence of CAD in women begins to increase (Fig. 4.1). This has led to the detailed study of the impact of female hormone changes at the menopause on the subsequent development of CAD in women. As women generally live longer than men, the universally asked question has been 'why do women live longer?', with a protective hormonal effect assumed to occur, whereas the alternative question 'why do men die earlier?' has not been addressed.

From 45 to 60 years of age, 1 in 5 men and 1 in 17 women will have experienced a coronary event. Over the age of 60 years, the incidence is equal at 1 in 4. Although the rate of developing CAD is less in women at any age, the greater number of older women compared with older men explains the similar absolute numbers. The incidence of CAD in women increases with age and though always less than in men the acceleration after the menopause underlines the need not only to study the impact of the menopause on CAD, but to recognize that CAD is as much a woman's as a man's disease. Indeed, the only practical difference is in the timing – 'when will she' rather than 'will she' be at risk of developing CAD. This assumes greater importance as the population ages and, as women constitute a

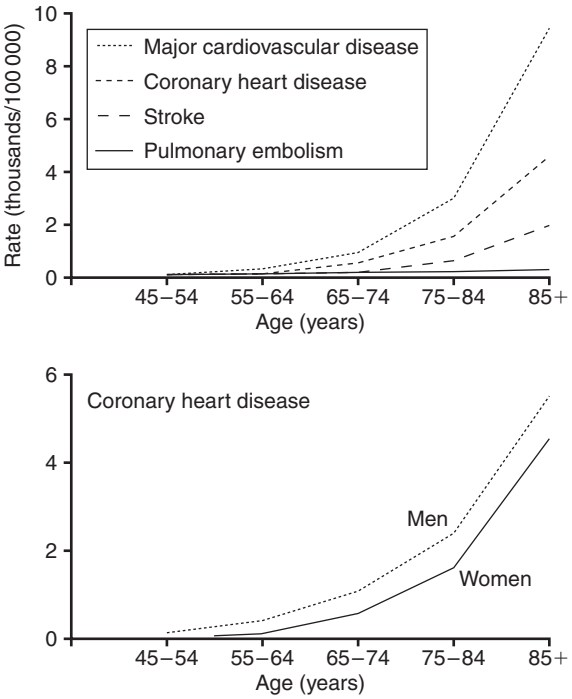

Figure 4.1
Mortality rises by age in both sexes. The male/female excess is 5:1 aged 35–44 years, but only 1.5:1 over 75 years. Though the relative risk declines, the absolute difference in CAD rates increases as CAD increases with age. Data reproduced from Lerner and Kannel 1986.[3]

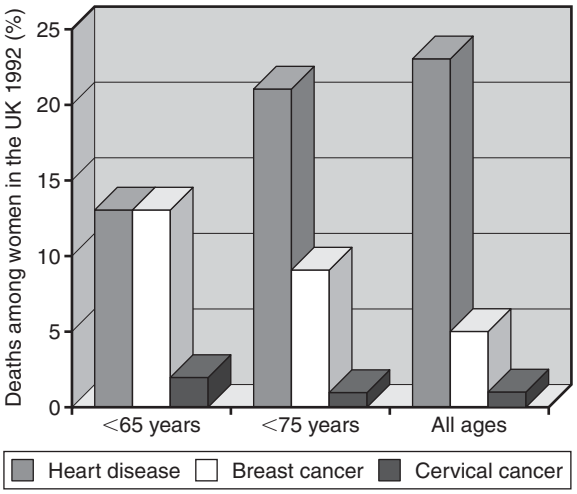

Figure 4.2
Ischemic heart disease and cancer deaths are approximately equal in younger women but over 65 years of age CAD is the major cause of death. Data reproduced from World Health Organization Annuals 1982–94. Geneva: WHO.

majority of that population, they are likely in the near future to represent the majority with CAD.[3] In the USA, older women outnumber older men and cardiovascular diseases in relative terms are a greater cause of death in women (46%) than in men (40%).[2]

Each year in the UK, 80 000 women and 100,000 men die from the consequences of CAD. In the USA, of 500 000 deaths from heart attack each year, over 230 000 are in women. In addition, 87 000 American women die each year from a stroke.[3,4] Cardiovascular disease claims more women's lives than cancer, trauma and diabetes combined, with cardiovascular deaths in women exceeding total deaths from all kinds of cancer two-fold (Fig. 4.2), and the much-feared breast cancer by four-fold in white women and six-fold in black women.

Many studies focus on death as the endpoint, but disability and quality of life are just as important. Cardiovascular diseases are now considered to be the principal cause of disability in women. It is estimated that one-third of women with coronary artery disease below 65 years of age are disabled as a result, and this increases to one-half in those over 65.[2,4]

Across all age groups, of the women who suffer a stroke, two-thirds are rendered permanently disabled.[2,4]

A recent Framingham report considered gender differences.[5] The differences in presentation are made more interesting by the better prognosis for women presenting with angina. This is almost certainly explained by a lower incidence of CAD (60–70%) in women at angiography compared with men (>90%).[1,5] Therefore, and not surprisingly, after 10 years' follow-up, subsequent myocardial infarction (MI) was twice as likely to be a problem in women initially presenting with infarction (34.8%) compared with women initially presenting with angina (17.8%).[5]

Women who have sustained an MI have a worse prognosis, probably as a result of increased age at presentation.[6,7] These patients are also more likely to have an increased risk factor profile with, in particular, an increased incidence of hypertension (49% women versus 35% men) and diabetes.[8] In women, the systolic blood pressure is secondary to age as the most important predictor of CAD, whilst in men it is fourth behind age, cholesterol and smoking.[3,9] As a consequence, a higher incidence of diastolic heart failure might be expected and this probably explains the paradox of higher ejection fractions in women post-MI, yet an increased incidence of heart failure.[4]

As the problem of CAD in women increases, the management problem and the clinical, as well as financial, burden of CAD in women will become of ever-increasing importance in the 21st century. It is self-evident that prevention should be a priority, not only in men, but also in women. Given the hormonal differences and the 10-year delay in women developing CAD, with the menopause appearing to be a watershed, attention has focussed on hormone replacement therapy (HRT) as a potential means of preventing CAD in women. As the majority of HRT studies have been with unopposed estrogen, ERT (estrogen replacement therapy) is often used instead of HRT.

Whilst this chapter will look at the evidence base for HRT, it should be noted that CAD also affects pre-menopausal women where the risk factors of diabetes, cigarette-smoking, hyperlipidemia and hypertension are as important as post-menopause.[10] No risk factor should, of course, be judged in isolation.[10] In a study of 51 female victims of sudden death, 30 women were less than 50 years of age and the most common risk factor was cigarette-smoking.[11] As 67% of all sudden deaths in women occur without any previous history of CAD, risk factor modification needs to be considered as a lifelong lifestyle change as well as a medical intervention.[1,2,11] Risk factor status should be routinely identified by the primary care physician. Just as cardiologists need to be alert to the symptoms of non-cardiovascular problems in their patients, so other physicians and surgeons need to be aware of the cardiovascular risks when dealing with non-cardiac problems.

The menopause and HRT: the theory

It is difficult to separate the effects of the menopause from the effects of age. However, the relationship between the onset of CAD and the menopause raises the question as to whether estrogen replacement may help prevent CAD. Before puberty, boys and girls have similar lipid levels, but after puberty LDL

cholesterol levels fall by an average of 0.13 mmol/L in young women and HDL levels fall by an average of 0.26 mmol/L in young men. These changes probably reflect the rise in androgen levels in boys and estrogen levels in girls.[12] Whilst the HDL differential persists into old age, although becoming less, the LDL differential gradually diminishes and is lost post-menopause.[12] Estrogen levels begin to fall gradually before the menopause. This fall in estrogen, coinciding with a rising LDL and falling HDL cholesterol, has led to the study of the relationship between hormonal changes (gradually occurring) and CAD development (gradually occurring).[13]

After abrupt early menopause caused by removal of the ovaries, women rapidly acquire a 2.2 times higher risk of CAD than age-matched pre-menopausal women. This risk is removed by immediate estrogen replacement therapy.[10] A naturally occurring menopause leads to a rise in LDL cholesterol of 10%, a fall in HDL cholesterol of 8% and a variable rise in triglycerides. Depending on type, HRT influences these lipid changes with quite significant differences between different regimes (Table 4.1). Evidence-based studies for one form of HRT cannot of course be extrapolated to another. HRT may also affect coagulation. Whilst the documented effect on fibrinogen – which is largely due to prevention of the post-menopause rise seen on placebo – may be beneficial, an estrogen-induced rise in factor VII_c may potentially lead to adverse effects.[13]

Studies of estrogen replacement have also suggested a direct effect on blood flow and arterial tone leading to vasodilation and increased blood flow. Endothelial-dependent and -independent effects on the vasculature have been identified.[14,15] However, the proposed calcium antagonism type action (endothelial-independent) would not suggest a prognostic benefit as calcium antagonists per se do not influence the prognosis of CAD.[15] These vasodilatory effects can be significantly reduced by progestogens which are often used in combination in women with an intact

	Oral estrogen 0.625 mg	*Transdermal combined preparations*	*combined oral HRT*	*Tamoxifen*	*Raloxifene*	*Tibolone*
TC	4–8%↓	–	8%↓	12%↓	6.4%↓	12–17%↓
LDL	12–19%↓	7%↓	14%↓	20%↓	10–12%↓	6–27%↓
HDL	9–30%↑	4%↑	11%↑	–	–	27%↓
Trig.	25%↑	13%↓	20%↑	–	–	34%↓
Lp(a)	20%↓	–	19%↓	32%↓	8%↓	26–48%↓
Fibrinogen	10%↓	–	10%↓	24%↓	12–14%↓	15–20%↓

Data collected from the literature and averaged.
TC, total cholesterol.

Table 4.1
HRT: effects on lipids.

uterus in order to avoid the endometrial proliferation which can affect 30% of women with an intact uterus who take unopposed estrogen.[15]

In summary:

- The menopause is associated with an adverse effect on the lipid profile
- This can be modified by HRT or, strictly speaking, ERT but different formulations have different effects (see Table 4.1)
- Other factors may influence risk and its modification by HRT, e.g. hemostatic status, endothelial actions
- Clinical trials are essential in order to see if these theoretical advantages of HRT translate into clinical benefit

The menopause and HRT: the trials

Observational studies

There have been over thirty observational studies which have suggested that postmenopausal women taking oral unopposed estrogen have a lower risk of developing CAD.[16] Combination therapy of estrogen plus progestin has not been as extensively studied, but similar protective benefits have been reported. The evidence for CAD benefit, has been the main focus for the reports, as outlined below. However, it is important to relate any CAD benefit to the risk of developing venous thromboembolism and cancer (breast or uterus). Any evidence of benefit with regard to cerebrovascular disease must also be assessed.

The Nurses' Health study

The Nurses' Health study is very widely reported and one of the largest and most thoroughly evaluated.[17] Commenced in 1976, it is a case control study that included 121 700 nurses aged between 30 and 55 years, 21 726 of whom were post-menopause. As the follow-up proceeded and an increasing number of subjects went through the menopause, their progress was widely reported.[17] It has been possible to look at the relationship between the menopause and cardiovascular disease development and the impact of HRT. Approximately half the women have not used HRT, women continuously on HRT represent 25%, and past users 25%. Of the HRT users, two-thirds were using unopposed estrogen and one-third a combined therapy.

In a recent analysis of 59 337 women with an average of 16 years' follow-up, there were 584 non-fatal MI, 186 coronary deaths, 572 strokes and 553 percutaneous or surgical revascularization procedures.[18] Current hormone users had a reduction in mortality compared with never-users, but this benefit was reduced with long-term use.[19] The risk for overall mortality was 0.63 (95% confidence interval [CI], 0.56–0.70) among current-users, reducing to 0.80 (95% CI, 0.67–0.96) after 10 or more years because of an increase in mortality due to breast cancer. The risk of major CAD in current-users versus never-users was 0.60 (95% CI, 0.47–0.76) and in past-users was 0.85 (CI, 0.71–1.01). Coronary revascularization procedures were equally common in hormone users and never-users. Current hormone users with increased risk factors for CAD had a greater reduction in death rates (relative risk 0.5 (95% CI, 0.45–0.57)), whereas subjects with minimal risk for CAD (13% of the total) had no mortality benefit.

There appeared to be no difference in the rate of risk reduction for CAD comparing estrogen alone with estrogen plus progestin.

The failure to influence revascularization procedures perhaps suggests the theoretical benefit on the endothelium does not translate into a clinical endpoint. As a concept, an early or even immediate beneficial effect on the endothelium might have been expected. An improved lipid profile is possibly an explanation for some of the benefit. The cardiovascular benefit continues beyond 10 years, even though the overall mortality benefit is lost because of the increased incidence of breast cancer.[19] The rapid loss of benefit in past-users, mostly after 3 years, may reflect the absence of a lipid effect on plaque stability.[20]

Of some concern is the absence of any beneficial effect on stroke risk, defined as non-fatal, and fatal cases caused by ischemic events, sub-arachnoid hemorrhage or intracerebral bleed. There were 121 strokes in current HRT users at a relative risk of 1.03 (CI 0.82–1.31) but a significant 40% excess occurred for ischemic stroke at 1.40 (1.02–1.92). Furthermore, there was a trend to a further significant increase with higher daily doses of estrogen (>1.25 mg), and estrogen alone was associated with a higher risk than estrogen in combination with progestin. Past-users had no excess risk, suggesting a direct link between ERT and ischemic stroke, perhaps due to a pro-coagulant effect.

Venous thromboembolism had a relative risk of 2.1 (CI 1.2–3.8) for current HRT use. This risk is short-term, which suggests an immediate adverse effect on coagulation and is more common in women at increased risk, e.g. the obese and those with peripheral venous abnormalities, but surprisingly not in cigarette-smokers.[21,22]

In a clinical context, the Nurses' Health study suggests:

- HRT reduces CAD risk
- HRT does not benefit stroke overall, but may increase ischemic stroke
- HRT increases the risk of venous thromboembolism, but only in the short-term

Observational studies are open to criticism. Women who take estrogen are healthier in general than those who do not: they weigh less, exercise regularly, smoke less, watch their health and take aspirin prophylaxis more often. These subjects self-select themselves and so create an obvious bias towards a healthier cohort who may coincidentally be taking HRT. Doing a meta-analysis of studies open to selection bias may not be a helpful exercise for obvious reasons. However, as it has been shown consistently that healthier women take HRT, the adverse effects on venous thromboembolism must be taken seriously as part of any subsequent trial program, as this is likely to be genuine rather than influenced by confounding factors. The possibility also arises of a bias caused by those women who stop HRT because they become ill, and so create a healthy survivor population who are the 'current-users' of HRT, i.e. making current-users appear even healthier.[16]

The PEPI trial

The drawback of estrogen alone (unopposed estrogen) is the increased risk of endometrial cancer when the uterus is intact. Pooled data identify a 2.3-fold higher relative risk, but no increased mortality (less invasive cancer). Combination therapy is, therefore, advocated when the uterus is intact. The Postmenopausal Estrogen/Progestin Interventions

(PEPI) trial was established to look at the differences between estrogen alone, combination therapy (three regimens) and placebo.[23] It was not a clinical endpoint trial, but focussed on risk factor modification. Treatment with oral estrogen produced the most favorable HDL changes, whereas combination therapies resulted in less favorable HDL changes. However, the results were still significantly better than with placebo. All active treatments reduced the LDL level by about 20% and the rise in fibrinogen on placebo was not seen on active therapy. There were no treatment differences in blood pressure, weight or insulin. One-third of women with an intact uterus who were allocated unopposed estrogen were withdrawn because of adenomatous or endometrial hyperplasia. The authors concluded that the maximum benefit relates to unopposed estrogen, but this should be confined to women who have had a hysterectomy. Combination therapy is essential when the uterus is intact. The PEPI trial did suggest that benefits were seen in addition to health consciousness as 'healthy women' were as frequently present in the placebo group.[24] However, the assumption that a reduction in risk factor profile translates into clinical endpoint benefit must be substantiated by randomized trials looking at clinical endpoints.

Other studies

The Lipid Research Clinics study at 8.5 years' follow-up found a five-fold reduction in death in HRT users with known CAD at commencement of HRT (66.3/10 000 versus 13.8/10 000), compared with a two-fold reduction in those commencing HRT without known CAD at baseline (mortality rate 12.8/10 000 versus 30.2/10 000).[25] The Leisure World study followed 8881 post-menopausal women for 7.5 years.[26] In women with no CAD history, all-cause mortality in estrogen-users was 21.8/1000 and 26.7/1000 in non-users, whilst in women with known CAD at entry the mortality rate was 27.5/1000 in estrogen-users versus 41.7/1000 in non-users.

Angiographic studies have found no difference between estrogen-users and non-users over 10 years if there was no CAD at baseline, but mild-to-moderate disease at baseline led to a 10-year survival of 85% in non-users and 96% in users ($p = 0.027$).[16] The benefit appeared to be greater the more severe the stenosis. In one series, 10-year survival after coronary artery bypass grafts was 81.4% in estrogen users versus 65.0% in non-users ($p = 0.0001$).[27] None of these studies, however, was on the background of current evidence-based risk reductions (e.g. statins, aspirin) and none were randomized prospective studies.

The need for randomized trial data

CAD is the most common cause of death in women so that, if HRT is beneficial with regard to CAD risk, any adverse effect on ischemic stroke and venous thromboembolism would be overcome by a greater benefit for the majority. However, if there were no CAD benefits, HRT could potentially be harmful as the adverse effects would assume prominence. The only way to resolve this dilemma is by means of randomized trials. However, these need to take into account the different cardiovascular effects of the HRT preparations (see Table 4.1) and the potential for adverse effects to appear early (venous risk inside 6–12 months) and beneficial effects to appear late (5–10 years for CAD).

The HERS trial

The Heart and Estrogen/Progestin Replacement Study (HERS) is a randomized trial designed to determine if estrogen plus progestin therapy alters the risk for CAD events in post-menopausal women with proven CAD.[28] A follow-up letter corrected the data presented in the paper and the revised figures are provided here.[29]

There are problems in comparing data in that the observational studies were predominantly in primary prevention and began at approximately 50 years of age, while HERS was a secondary prevention trial (i.e. all had CAD), and the average age was 67 years. There are other major differences: the duration of the HERS trial was short (average 4.1 years), at entry the mean LDL cholesterol was 3.75 mmol/L (which is significantly raised), nearly 20% of subjects were diabetic, the time since the menopause averaged 18 years, exercise was undertaken by only 35%, and 57% were overweight. In addition, 24% reported their general health to be poor or fair. A cardiologist might reasonably argue that initiating HRT in this population was wholly inappropriate and that focusing on evidence-based secondary prevention should have been the priority.

The HERS trial enrolled 2763 women and randomized them to 0.625 mg conjugated equine estrogen plus 2.5 mg medroxyprogesterone acetate, or placebo. The primary endpoint was non-fatal MI or cardiovascular death. HRT produced the expected lipid changes with a reduction in LDL cholesterol of 11%, a rise in HDL of 10% and in triglycerides of 8%. In patients with CAD, the statin trials identified the need for a 25–35% fall in LDL cholesterol to generate a significant and relatively quick impact on coronary events.[20] It is therefore not surprising that these modest changes failed to benefit the primary endpoint quickly. Of note, however, in the first year there were more CHD events in the HRT group (57) than in the placebo group (38; $p < 0.05$), whereas in the second year there were no differences. By the end of the study there was a trend in favor of the HRT group, mainly because of a reduction in non-fatal MI. There were no benefits in other CHD outcomes, including revascularization procedures. The venous thromboembolism event rate was significantly higher in the first year only (34 vs 13; $p = 0.0002$), in line with the observational findings. There was a non-significant excess of gall bladder disease, but this was not screened for at entry and there was no difference in the incidence of fractures.

The first year's vascular findings may be explained by the known procoagulant effect of HRT, to which some women are susceptible. Although the venous thromboembolic rate overall was higher in the HERS trial, caused by the higher risk population, the proportionate difference between HRT and placebo was similar to that found in the observational studies. The later CHD benefit with time may reflect an effect on the endothelium similar to the statins whose surrogate for plaque stabilization is LDL cholesterol reduction. The authors of the HERS trial concluded: 'we do not recommend starting this treatment for the purpose of secondary prevention of CHD'. This is proven for their subject group who were older, overweight, took little exercise and had a history of CHD.

HERS analysis

The HERS trial illustrates the importance of randomized trials and the role of evidence-based medicine. Table 4.2 summarizes current evidence for risk reduction in women with, or

	Primary prevention	*Secondary prevention*	*Comment*
Smoking cessation	Yes	Yes	Cheap
Weight reduction	Yes	Yes	Cheap
Aerobic exercise	Yes	Yes	Cheap
Blood pressure control	Yes	Yes	Target <140/90 mmHg
Lipid-lowering therapy	No	Yes	Significant
Beta-blockers	No	Yes	Selected cases
ACE inhibitors	No	Yes	Selected cases
Aspirin	No	Yes	Cheap
PTCA	N/A	No	Symptomatic benefit only
CABG	N/A	Yes	Selected cases

PTCA: percutaneous transluminal coronary angioplasty.
CABG: coronary artery bypass grafting.

Table 4.2
Evidence-based risk reduction (other than HRT) for women.

Treatment	*HRT (%)*	*Placebo (%)*	*Evidence-based benefit (%)*
Aspirin	78	78	Yes, 25
Lipid-lowering therapy	45	47	Yes, 40
Beta-blockers	33	32	Yes, 25
Calcium antagonists	55	55	No
ACE inhibitors	17	18	Yes, 20
Diuretics	28	28	No
Multivitamins	29	30	No

Table 4.3
HERS trial and use of evidence-based medicine.[28,29]

at risk of, CAD. It is important, however, to maintain a degree of objectivity and perspective. The HERS trial was stopped too soon and has introduced confusion rather than clarified the role of HRT. The HERS trial does, however, highlight the under-use of evidence-based medicine. Aspirin was used in 78%, lipid-lowering therapy in 45%, beta-blockers in 33% and angiotensin converting enzyme (ACE) inhibitors in 17% – all therapies with proven benefit in this population. Calcium antagonists were used in 55% and multivitamins in 30% – therapies of no proven benefit (Table 4.3).

The increased incidence of venous thromboembolic disease (three-fold) is as predicted, but in higher numbers. HRT does appear to have a procoagulant effect which, if genuine, would be expected to occur early (which it does) in a susceptible high-risk group already suffering from CHD. At present we have no means of identifying these women, so the recommendation not to use HRT as a means of secondary prevention in women with CHD makes sense, particularly as we have proven beneficial therapies which are under-used to an alarming degree.

It is difficult to interpret the non-significant gall bladder data as the women were not screened at entry.

The 'cardiologic gynecologist' and the 'gynecologic cardiologist', however, need not be afraid of HRT. HERS could be interpreted as identifying the need to initiate HRT when the risk of venous thromboembolism is low (supporting the observational studies), so that the benefits will be available when the CHD incidence is high and venous thromboembolic risk no longer a problem. The HERS trial suggests the following evidence-based recommendations:

- HRT is not a proven means of preventing or treating CHD and cannot be recommended for this indication
- Proven beneficial treatments need to be prioritized and their use audited
- HRT is not a first-line therapy for hyperlipidemia as there are no clinical endpoint data to support this indication. It may be a second-line agent, e.g. in addition to a statin or fibrate
- Women on HRT should continue unless there are specific concerns. There is no general cardiovascular indication to stop therapy in the face of proven osteoporosis and vasomotor symptom benefits
- Women being considered for HRT should be advised on an individual basis when CHD is present. HRT can only be advocated from the cardiac viewpoint in addition to proven secondary prevention measures
- As there is no evidence that any particular HRT formulation is better or worse than another regarding cardiovascular endpoints, the choice of agent should be made on an individual basis.

The ERA trial

The Estrogen Replacement in Atherosclerosis trial randomized 309 women with angiographically proven CAD to receive 0.625 mg of conjugated estrogen plus 2.5 mg of progesterone per day or placebo.[30] The subjects were followed for a mean of 3.2 ± 0.6 years and the primary endpoint was progression of CAD as measured by quantitative angiography. The authors found no difference between all three strategies in the primary angiographic endpoint and also no difference in clinical events. They concluded that 'such women should not use estrogen replacement with an expectation of cardiovascular benefit'.

It is important once more to note that this is a secondary prevention trial, with the HRT being introduced approximately 23 years after the menopause in women averaging 65 years of age. The duration of the study was short (mean 3.2 years) so little time was allowed for any impact on plaque stability regarding clinical endpoints. Angiographic appearances do not let us know whether the plaque is lipid rich with a thin fibrous plaque and therefore vulnerable or whether it is stable.

The baseline characteristics of the women

in this small study were substantially different from those in the observational studies. In the ERA study, 25–30% were diabetic, 60–70% hypertensive, 20% smokers, 55–60% overweight and 40–50% physically inactive. Once more evidence-based medicine was not fully employed. Therapy of proven prognostic benefit (crude averages) included 72% on aspirin, 45% on betablockers, 37% on lipid lowering agents and 23% on ACE inhibitors. In contrast, 57% were on calcium antagonists, 40% on nitrates and 30% on diuretics – therapies with no proven prognostic benefit.

There are other problems with this study – it is short, the women were old at entry and, in the absence of established secondary prevention measures, clinical endpoints in such a small study cannot be relied on, especially when they are not the primary endpoint. The authors use the statin data which relates angiography to clinical endpoints but fail to take into account the degree of LDL cholesterol lowering needed.[17] In the ERA trial, the estrogen group had a reduction in LDL of $9.4 \pm 20.9\%$, the combined group $16.5 \pm 21.8\%$ and placebo $1.3 \pm 21.5\%$, with HDL rising to $18.8 \pm 20.8\%$, $14.2 \pm 17.1\%$ and $6.8 \pm 15.6\%$ respectively. These wide confidence limits reflect the small numbers in the study and do not equal the LDL reduction needed according to the statin studies (25–30%).

Once more it is also necessary to remember not to extrapolate data from one form of HRT to another. Whilst it is not reasonable to extend from the HERS and the ERA observation regimes without formal randomized studies, it is reasonable once more to highlight the need to use established treatments optimally.

The authors of ERA 'believe at least one conclusion can now be reached about cardiovascular effectiveness of hormone replacement therapy: in women with established coronary artery disease, the most commonly used form of hormone replacement therapy in the United States does not appear to reduce the risk of clinical cardiovascular events (as shown by HERS) or slow the progression of the underlying disease process responsible for these events (as shown by ERA)'.[31] These findings are made on a limited basis. They were shown in older, overweight, high-risk individuals who were relatively inactive and who began HRT therapy 23 years after the menopause for a short period of time. Nor were evidence-based prognostically important treatments given to sufficient numbers in the group.

HERS and ERA complicate, rather than ease, the clinical debate about HRT and cardiovascular risk. The Women's Health Initiative trial should clarify some urgent clinical issues. There is enough evidence regarding a healthy lifestyle[32] and selective pharmacology to allow a redoubling of efforts – HERS and ERA clearly show that there is a lot still to do.

The study illustrates the importance of randomized trials and the role of evidence-based medicine. Table 4.2 summarizes current evidence for risk reduction in women with, or at risk of, CAD.

In secondary prevention trials, in the presence of therapies that provide evidence-based risk reduction, a new therapy will take time to impact on endpoints, unless dramatically effective. However, adverse effects may appear early and distort any concept of long-term value. In contrast, in primary prevention trials, the absence of competing prevention strategies allows for easier recognition of any benefit. Treatment and evidence-based benefit is compared between women with and without CAD

Treatment	*Women with CAD (%)*	*Women without CAD (%)*
Aspirin	25	–
Lipid-lowering therapy	46	–
Beta-blockers	25	–
ACE inhibitors	20	–
Hormone therapy	Tough challenge	Clear run

Table 4.4
Treatment and evidence-based benefit is compared between women with and without CAD. In the presence of established therapy a new therapy will have a tough challenge. Where there is no evidence there will be a 'clear run'.

(Table 4.4). Furthermore, the findings cannot be extrapolated to other patient groups or estrogen therapies because of the different cardiovascular effects (see Table 4.1).

Breast cancer

The fear of cancer, especially breast cancer, is understandable. The Nurses Health study found an age-adjusted increase in the relative risk for breast cancer in women on unopposed estrogen (relative risk 1.36) and combination therapy (relative risk 1.50).[33] This risk increased with the duration of HRT so that after 10 years of therapy the increased risk of death from breast cancer reduced the cardiovascular benefit from 50% to 20%. The relative risk appears to rise from year 5 onwards, especially in women over 60 years of age. The addition of progestin does not reduce the risk.[34] Claims that the type of breast cancer is less invasive may reflect early detection rather than a direct effect. At present women are not recommended to commence HRT if they have a personal history of breast cancer or have a strong family history that affects a first degree relative.

- There is no proven benefit for starting estrogen alone or with progestin for reducing CAD risk.
- Estrogen increases the risk of venous thromboembolism two- to four-fold, but the absolute risk is low. The risk occurs inside the first 12 months and there is no recorded long-term risk. A pro-coagulant effect is the likely cause.
- Estrogen increases the risk of breast cancer after 10 years of therapy (observational data) and cannot at present be recommended for women with a personal or close family history of breast cancer.
- HRT benefits osteoporosis and vasomotor symptoms and its use must be individualized, taking into account the pros and cons.
- SERMS are attractive as a concept, but need thorough evaluation and clinical cardiac endpoint data.
- A woman taking HRT must be fully informed of the potential benefits and disadvantages.

Table 4.5
HRT and cardiovascular disease: evidence-based guidelines.

SERMS

Selective estrogen receptor modulators (SERMS) are a new class of agents designed to select out the benefits of HRT on bone and the heart whilst avoiding the breast and uterine cancer risk.[34] Tamoxifen was the first of the SERMS used in clinical practice. The only disadvantage with SERMS as a routine HRT is the absence of any beneficial effect on the menopausal vasomotor symptoms and the possibility of endometrial stimulation.[36]

Tamoxifen

Tamoxifen has been shown consistently to lower serum cholesterol in post-menopausal women with breast cancer.[37] In one study, the mean decrease in total cholesterol was 12% and the mean decrease in LDL cholesterol 20%, whereas HDL was largely unaffected.[38] Of interest, women with greater baseline cholesterols had greater decreases with tamoxifen. There is, of course, no point in pursuing these interesting findings unless they translate into clinical benefit.

In a long-term study on breast cancer risk, tamoxifen reduced CAD mortality by approximately 50%.[39] In another study of post-menopausal women with early stage breast cancer, tamoxifen significantly reduced hospital admissions caused by cardiac disease, combining a substantial reduction in cardiac morbidity over 2–5 years of 32% with a low risk of death from breast cancer.[40] As an adjuvant treatment for breast cancer, tamoxifen reduces mortality by 25% and contralateral primary breast cancer incidence by 40%.[35] The benefit on breast cancer continues, with evidence of protection against post-menopausal bone loss and reduced cardiovascular mortality, but there is a two- to six-fold increase in endometrial cancer.[36] In absolute terms, this represents an increase from one to two cases of endometrial cancer per 1000 tamoxifen-treated women per year. While screening costs will be incurred, the incidence of endometrial cancer relative to the cardiovascular benefit with no adverse breast cancer risk makes tamoxifen an attractive alternative HRT, providing vasomotor symptoms are not a limiting factor.

In those with breast cancer or at increased risk of breast cancer, perhaps tamoxifen could be considered the HRT of choice, and certainly in those who have undergone a hysterectomy. In addition, should those at increased cardiovascular or bone loss risk who have completed 10 years of conventional HRT be switched to tamoxifen to enable them to continue to benefit without the breast cancer risk?

Raloxifene

Raloxifene is the second SERM to become available. There is a less beneficial effect on lipid profiles, compared with estrogen, with no effect on raising HDL cholesterol (see Table 4.1).[41] Indicated for osteoporosis at present, cardiac endpoint trials are underway. Raloxifene differs from tamoxifen in avoiding endometrial stimulation so it presents an attractive concept in women with an intact uterus.

Conclusion

CAD is the most common cause of morbidity and mortality in women. It is an equal-opportunity killer that needs equal-opportunity management. Established evidence-based approaches to prevention and optimal treatment are under-employed.

- Gynecologists may see women who are at risk of developing CHD but have no cardiac symptoms. Screening their blood pressure, glucose and lipids along with lifestyle advice would be good medical practice.
- Women with CHD who are on HRT should be managed jointly by a gynecologist and cardiologist.

Although at present HRT cannot be recommended as an alternative therapy to established evidence-based risk reduction treatments for CAD in women, it does not need to be discontinued in those already taking HRT because there is no evidence of a deleterious cardiovascular effect.[28] In addition, cardiac patients vulnerable to osteoporosis or who have vasomotor symptoms remain candidates for HRT provided that their venous thromboembolism and breast cancer risk is carefully assessed and the patient counselled on the pros and cons of therapy.

Given that a woman may spend one third of her life post-menopause, it is imperative that randomized studies continue with the various HRT preparations, including SERMS, in the hope that one will be the key to the door that may open for HRT and coronary prevention. Until then, there is no cardiovascular mandate for HRT – the task is to monitor continually the trials that are under way so that any benefit is immediately identified.

In answer to the question: 'are cardiovascular benefits established?' – the answer is 'no'. Optimists would say 'not yet', fence-sitters 'await the trials', the uncertain 'wait and see', but there is a need to be practical, the answer now is 'no'. Fortunately, further large-scale trials remain in progress. Hopefully these will clarify the areas of uncertainty that continue to surround the role of HRT/ERT – for women's sakes, let us hope that the current 'no' becomes a future 'yes'.

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5

Alcohol, Hypertension and Cardiovascular Disease

Gregory YH Lip, Eiry Edmunds and D Gareth Beevers

Introduction

Man's use of alcohol for recreational purposes pre-dates written history and references to its use and misuse can be found in ancient writings. It is increasingly recognized that alcohol has many effects on the cardiovascular system. Both acute and chronic alcohol consumption can influence blood pressure, but more prolonged, excessive usage can lead to alcoholic heart muscle disease. Heavy binge drinking is also one common precipitant of cardiac arrhythmias, such as atrial fibrillation.

Alcohol and hypertension

The association between alcohol and hypertension has been recognized since 1877 when Frederick Akbar Mahomed of Guy's Hospital, London, noted that there was 'a high tension' pulse in '. . . apparently healthy persons, but who, not uncommonly are subject of the gouty diathesis, dyspeptics, alcoholists . . .'.[1] In 1915, Lian measured blood pressures in 150 French soldiers and observed that those who were 'sober' (that is, those who drank less than 1 litre of wine a day) had a lower prevalence of hypertension than the 'very great drinkers' (those who drank over 3 litres of wine a day) (6.25% vs 25%).[2]

Following Lian's observations, the relationship between alcohol and hypertension was largely forgotten until 1959 when Edwards et al reported higher mean blood pressures in a cohort of 1045 male Birmingham drinkers when compared to their non-drinking fellow citizens.[3] In the same year, a study of male drinkers aged between 35 and 75 in Bombay, India was published by Shah and Kunjannan.[4] At that time in Bombay State, drinkers had to apply for a drink permit and so were conveniently to be found on a state register. This study reported that 1029 drinkers had higher mean blood pressures than 996 controls. Since then, the relationship between alcohol and blood pressure has been studied in many epidemiologic and intervention studies.

Alcohol and blood pressure: studies

Cross-sectional population studies

Many cross-sectional population studies have investigated the association between alcohol and hypertension. In 1977, the Kaiser-Permanente Multiphasic Health Examination study reported that, of their cohort of 83 947 subjects, the mean blood pressure of men who drank 6 or more drinks a day was 10.9 mmHg higher than that of non-drinkers and this effect was independent of age, gender, educational level, racial grouping,

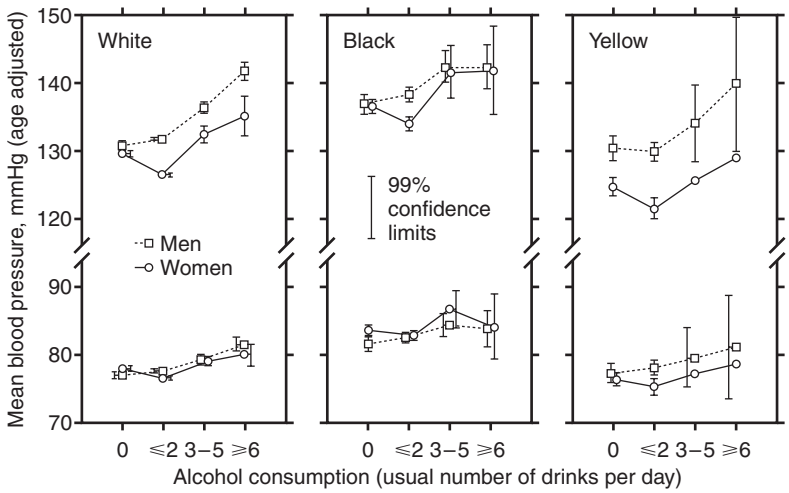

Figure 5.1
Alcohol consumption and blood pressure in the Kaiser-Permanente Multiphasic Health Examination Study 1977. Reproduced with permission from Klatsky et al 1977.[5]

obesity or cigarette habit (Fig. 5.1).[5] Similarly, the Framingham study reported that, of a cohort of 5209 subjects, heavy drinkers were twice as likely to have hypertension compared to light drinkers.[6] In 1994, the multi-national INTERSALT study studied alcohol consumption in a cohort of 4626 men and 4647 women aged 20–59 years in 32 countries, and found that men who drank 300–499 ml of alcohol per week had average systolic and diastolic blood pressures of 2.7/1.6 mmHg higher than non-drinkers.[7] Men who drank >500 ml of alcohol per week had mean blood pressures 4.6/3.0 mmHg higher than non-drinkers, whilst women who drank >300 ml of alcohol per week had mean blood pressures of 3.9/3.1 mmHg higher than non-drinkers. These findings have since been corroborated in many studies from other centers.

Approaching the question from another angle, Beevers found that patients in Renfrew, Scotland with raised blood pressure had a higher frequency of liver enzyme abnormalities when compared to age- and sex-matched normotensive controls, which suggests heavier alcohol usage.[8] Practically, all cross-sectional population studies have demonstrated a direct significant relationship between alcohol intake and blood pressure.

Prospective studies

There have been several well-conducted prospective observational studies, which have supported the findings of an association of blood pressure with alcohol consumption. One of the earliest was the Chicago People's Gas Company study which found that at baseline, 'problem drinkers' (although there was

no quantification of the amount) had a greater prevalence of high blood pressure (defined as >160 mmHg systolic or >95 mmHg diastolic) when compared to non-problem drinkers (47.4% vs 23.2% respectively).[9] At the 4-year follow-up, the problem drinkers had a greater increase in blood pressure than non-problem drinkers.

The Chicago Western Electric Company study reported similar findings in heavy-drinkers, where in 1899 white male employees the base-line blood pressure (both systolic and diastolic) was much higher in men who consumed >6 drinks per day.[9] After 4-years follow-up of a normotensive cohort, the heavy drinkers had a significantly higher incidence of hypertension than the lighter drinkers. In the American Nurses' Study, which followed 58 218 nurses for 4 years, those drinking more than 20 g alcohol per day had a significantly increased risk of developing hypertension and this increased risk was dose-dependent.[10]

In 1973, Nakayama et al looked at a group of hospitalized men and followed them up over a period of 2–11 years. In that time, it was found that the blood-pressure at follow-up was associated with base-line alcohol consumption.[11] The Framingham investigators also reported that those who increased their alcohol consumption during follow-up were more likely to develop hypertension, whereas those who reduced their consumption had lower blood pressures.[12]

Interventional studies

Further to the epidemiologic data summarized above, a direct and causal relationship between alcohol consumption and blood pressure has been suggested by a few interventional studies. Saunders et al in 1981 studied 132 alcoholics (>80 g alcohol per day) who were admitted to hospital for detoxification.[13] Following a period of abstinence in hospital, the proportion of patients with a blood pressure >140/90 fell from 51% to 9%. Those patients who continued to abstain remained normotensive, but in those who started to drink again, the mean blood pressure rose. This study suggested that the effects of alcohol on blood pressure were direct and reversible, but the study was criticized for not having a control arm.

In a subsequent study, Potter and Beevers observed eight moderately hypertensive men who drank six to eight drinks per day abstained for 4 days.[14] Mean blood pressures remained high whilst alcohol consumption was maintained, but fell significantly when alcohol was withdrawn. In a second group of eight patients who abstained for 4 days, blood pressures rose on resuming their normal alcohol intake (Fig. 5.2). Later, Maheswaran et al were able to demonstrate a blood pressure lowering effect of alcohol counselling in the clinical environment.[15]

Other investigators have also confirmed the alcohol/blood-pressure relationship in interventional studies. For example, Puddey et al in 1985 found a significant fall in the blood pressure of normotensive drinkers (an average of 5 drinks per day) when alcohol was restricted in a cross-over study.[16] Again, the blood pressure increased when regular drinking resumed. Similar results were obtained in treated hypertensive patients.[17] In 1985, Malhotra et al studied ten normotensive subjects, ten hypertensive subjects who were 'special occasion only' drinkers and ten hypertensive subjects who drank moderate amounts of alcohol (up to 60 g daily).[18] In this study, 5 days of alcohol consumption (1 g alcohol per kg body weight per day) had no effect on the blood

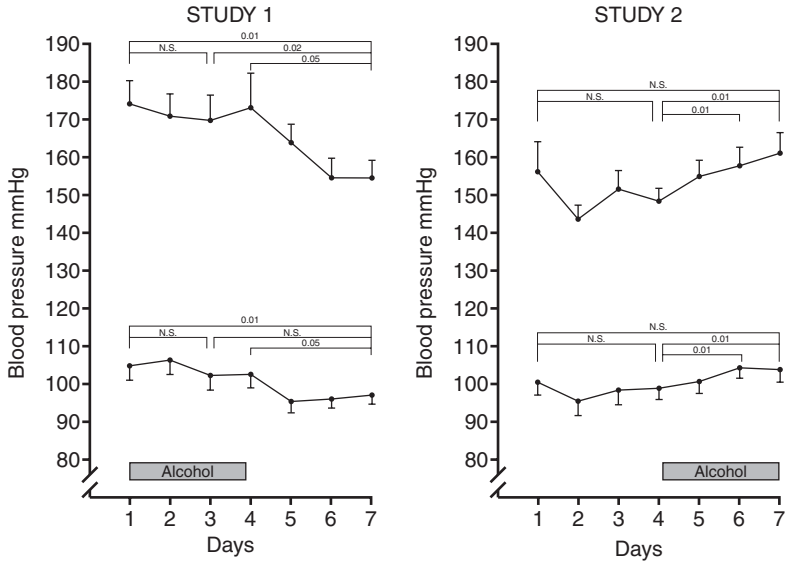

Figure 5.2
The effects of alcohol consumption and abstention on blood pressure in hypertensive patients. Reproduced with permission from Potter and Beevers 1984.[14]

pressure of normotensive subjects but caused a significant increase in blood pressure of hypertensive non-drinkers. In contrast, abstinence resulted in a significant decrease in blood pressure amongst hypertensive drinkers.

Alcohol and blood pressure: effects

The many cross-sectional, prospective and interventional studies strongly support the hypothesis that alcohol has a direct, reversible effect. Studies by Puddey et al[16,17] and Saunders et al[13] suggest that the pressor effect on blood pressure occurs within days of starting ingestion, but disappears soon after abstaining. There remains, however, much controversy as to whether the relationship is a linear one, J-shaped or even U-shaped.

Some authors have even suggested that there is a threshold of alcohol consumption below which there is no effect on blood pressure.[19] In the first Kaiser-Permanente Study, there was no difference in the blood pressure of men consuming one to two drinks per day compared with non-drinkers, which suggests that there may be such a 'threshold'.[5] Amongst the women in this study, non-drinkers had higher blood pressures than those who consumed one or two drinks per day, which may imply the existence of a J-shaped curve in some populations. A J-shaped curve was reported from the male cohort of the Framingham study, although a U-shaped curve was found in the women, with blood pressure in non-drinkers being similar to those with highest alcohol consumption.[11] A plateau

effect was nevertheless observed in black male drinkers in the first Kaiser-Permanente study but no such effect was seen in white males in the second study.[20] The Chicago Western Electric Company Study[9] and Arkwright et al[21] reported a linear relationship between alcohol and blood pressure, with no threshold.

In order to explain the different findings in the many studies, the different characteristics of the study populations must be considered. Some studies looked only at hypertensive subjects, whilst others looked at only alcoholics or problem drinkers. There were also differences in the methods of collecting data on alcohol consumption, such as self-reporting in questionnaires, or direct questioning by investigators. Differences in how the quantity of alcohol consumed was described (such as the number of drinks per day, number of ounces or grams per week, etc) and differences in categorizing patients (as non-drinkers, ex-drinkers, moderate drinkers and heavy drinkers) are also apparent when the different studies are carefully reviewed.

It is likely that any errors in reporting alcohol consumption would tend to be due to under- rather that over-reporting. This would result in an under- rather than over-estimation of the relationship. Denial of alcohol consumption by heavy-drinkers may contribute to the J-shape sometimes seen. In some studies, the non-drinkers may have included former heavy-drinkers as well as life-long teetotallers. This may affect the findings since the ex-drinkers may have given up drinking because of medical conditions, such as hypertension. Alcohol consumption is only one of many clinical variables that affect blood pressure and, in order to obtain more information on the relationship between alcohol and blood pressure, the other variables need to be taken into consideration.

Alcohol and blood pressure: influencing factors

Ethnicity

Many of the cross-sectional population studies have been performed in the United States (Kaiser-Permanente,[5] the Chicago Studies,[9] Framingham[6]), but studies performed in Europe (Cairns,[22] Kornhuber,[23] Milton[24]), Australia and New Zealand (Arkwright,[21] Savdie[25]) India and Japan (Ueshima,[26] Kondo and Ebihara,[27] Wakabayashi[28]) have consistently shown the relationship to hold true in different races.

Blood pressure is often higher in blacks compared in whites, and this could affect the relationship between alcohol consumption and blood pressure. For example, the Kaiser-Permanente Study divided the subjects into 'white', 'black' and 'yellow' and found the relationship to be similar in white and yellow men but weaker in blacks.[29] This study also found a plateau effect in black men with no progression in the alcohol–blood pressure relationship beyond three to five drinks per day. In the Japanese studies, there was a more marked relationship at lower levels of alcohol consumption, which may perhaps reflect genetic variation in the expression of aldehyde dehydrogenase and the consequent accumulation of acetaldehyde.[26] In Orientals with reduced levels of this enzyme, the acute effect of alcohol consumption is vasodilation and hypotension.[30]

Gender

Most of the studies have included both men and women in their analyses but the numbers of heavy-drinking females have usually been smaller than males which may weaken the results.[29] The studies by Klatsky et al,[29]

Arkwright et al,[21] Wannamethee and Shaper[31] and others have shown a weaker association between alcohol and hypertension in women than in men. In the Kaiser-Permanente Study,[29] for example, the mean systolic blood pressure difference between those taking six or more drinks per day and non-drinkers was 5.4 mmHg in women compared to 10.9 mmHg in white men.[29] The study by Paulin et al reported a significant relationship between alcohol and blood pressure in men but not in women.[32] In a number of studies, such as the Lipid Research Clinics Prevalence Study by Criqui et al,[33] a curvilinear relationship between alcohol and blood pressure was seen, especially in older women.

There may be other confounding factors that influence the relationship between gender and blood pressure, such as obesity, the use of the oral contraceptive pill, menopausal status, or the use of hormone replacement therapy.[34]

Age

Blood pressure usually increases with age[35] and it is therefore important to take age into account in any analysis of hypertension studies. Studies such as those by Dyer[9] and Puddey[16] have stratified their results according to the age of the subjects. Most have shown that the relationship between alcohol and blood pressure is stronger in older people (such as in the second Kaiser-Permanente study[20]). The altered relationship at different ages may be due to differing biologic responses or due to the delayed effect of alcohol on blood pressure.

Obesity

The association between obesity and elevated blood pressure has been consistently reported.[21] Suter et al found that, in a group of 842 non-smoking men, the increase in weight over a period of about 30 years was related to the quantity of alcohol consumed.[36] As the blood pressure increased with increased alcohol intake and waist-hip ratio, some of the effect of alcohol on blood pressure may have been due to alcohol-induced accumulation of abdominal fat. In the Kaiser-Permanente study, however, Klatsky et al found that, in the women studied, the non-drinkers were the most obese and those who drank modestly were less obese. Interestingly, in black men and women there was no association between drinking and adiposity, whereas in white, male, heavy drinkers there was a positive correlation.

Arkwright et al found the two variables to have an additive effect on blood pressure, but alcohol intake was a slightly stronger determinant of systolic pressure than was obesity.[21] The Kaiser-Permanente study also found that high alcohol consumption and adiposity were significantly but independently related to higher blood pressure in white men.[5,29] If the subjects were stratified according to adiposity, then the relation of alcohol intake of three or more drinks per day to higher diastolic and systolic blood pressure remained.

Smoking

Heavy drinkers are more likely to be smokers. In the Perth study by Arkwright et al, 18% of teetotallers were smokers compared to 50% of men who drank more than 350 ml/week of alcohol.[21] Some studies, such as that by Arkwright et al[21] and the Kaiser-Permanente study[5,29] have shown a negative association between smoking and blood pressure. In the Perth study, teetotallers who smoked had mean diastolic pressures which were on average 5.8 mmHg lower than those who did

not smoke.[21] Similarly, heavy drinkers who smoked had diastolic pressures which were on average 4.9 mmHg lower than those who did not smoke. The INTERSALT study found that if the data for smokers and non-smokers were analysed separately, the relationship between alcohol consumption and blood pressure was not lost.[7] Wakabayashi et al also showed that smokers had lower blood pressure than non-smokers.[28] This may be due partly to a lower incidence of obesity in smokers.[12] In the Perth study, however, the depressor effect of smoking was present even when the degree of obesity was constant.[21]

It is important to take into account the confounding effects of smoking on blood pressure in any analysis of the relationship between alcohol and blood pressure. If smoking causes a lowering of blood pressure, and drinkers are more likely than non-drinkers to smoke, then smoking would lead to an underestimation of the effect of alcohol on blood pressure.

Physical activity

The relationship between alcohol and blood pressure may be confounded by physical activity, because physically inactive or sedentary subjects have a greater chance of developing hypertension than active subjects.[37] Jenner reported that there was an inverse relationship between blood pressure and physical activity.[38] Other investigators have also reported that those who take part in sporting activities had higher alcohol consumption than those who do not regularly do sports. In the Perth study, 46% of teetotallers said that they exercised regularly compared with 65% of men who drank more than 350 ml/week.[17] Arkwright[21] and Williams[39] found that, when adjusted for smoking, age and Quetelet index there was no effect of regular exercise on blood pressure.

Type of beverage

The direct relationship between alcohol intake and blood pressure has been found in many populations including those whose main alcoholic beverage is either beer, spirits, wines or Japanese rice wine. This strongly suggests that it is the alcohol itself rather than the beverages in which it is consumed which raises the blood pressure.[12,26,32]

However, the second Kaiser-Permanente study found that subjects who preferred wine had the lowest systolic pressure levels, those who preferred beer had the lowest diastolic pressures, and those who preferred hard liquor had the highest systolic and diastolic pressures.[20] Whilst the type of alcoholic beverage consumed may influence the amount of alcohol per drink, other confounding factors may be present, such as lifestyle traits and whether alcohol is consumed with food, thus blunting the effect of an acute alcohol load. Potential confounders should thus be considered when examining the relationship between alcohol, blood pressure and type of beverage. However, acute alcohol-loading studies also suggest that it is the alcohol itself which raises the blood pressure, rather than the type of beverage, as alcohol-free beer did not raise blood pressure unless alcohol was added to it without the subject knowing.[40]

Pattern of drinking

The INTERSALT study suggested that heavy-drinking men who had a low daily variability of alcohol intake had relatively small and non-significant blood pressure variation, similar to differences in comparison with non-drinkers. By contrast, heavy-drinking men whose drinking pattern was much more variable had more variable blood pressure.[7] Wannamethee and Sharper, similarly, found that heavy weekend

drinkers had higher mean blood pressures when compared to moderate daily drinkers, although their total weekly alcohol consumption was similar.[31] They also reported that higher mean blood pressure levels were more prevalent on Mondays than Fridays in 'weekend' drinkers and was higher throughout the week in daily drinkers. Criqui found that alcohol consumed in the 24 hours before the study was more strongly associated with elevated blood pressure than that consumed during the week.[33]

Stress

Psychological stress can predispose to a rise in both blood pressure and alcohol abuse.[41–43] The degree of psychological stress is difficult to measure but attempts to incorporate stress into the analysis have been done. For example, Schnall found that drinkers in 'high-stress' jobs had higher systolic blood pressures than those in less stressful jobs.[42] In contrast, Arkwright in the Perth study found that alcohol consumption was independent of type A behaviour, anxiety traits, recent life stresses and introvert/extrovert personalities.[43]

Alcohol and blood pressure: mechanisms

Although it is now widely accepted that alcohol has a direct and causal effect on blood pressure, the precise mechanisms by which alcohol exerts this pressor effect remain poorly understood (Fig. 5.3).

Central nervous system stimulation

In susceptible people, alcohol could have a pressor action by interfering with the central inhibitory pathways that control vasomotor centres, in a similar manner to the action of alcohol on higher cortical functions, leading to loss of emotional control. Randin et al found that, following an infusion of alcohol, there was an increase in discharges from sympathetic nerves which was accompanied by an elevation in blood pressure and which was abolished by dexamethasone, thus suggesting a centrally mediated sympathetic response.[44]

Catecholamine response

The pressor effect of alcohol could be related to catecholamine responses that follow alcohol intake. For example, plasma levels of epinephrine increased immediately following alcohol ingestion in normotensive men.[45] It has therefore been proposed that regular ingestion of alcohol could cause repeated activation of the sympathetic system, which would thus be responsible for a 'slow pressor' response and chronic elevations of blood pressure.

Howes and Reid found that alcohol administration was associated with a transient increase in blood pressure which preceded an increase in plasma norepinephrine and was associated with a fall in the norepinephrine intraneuronal metabolite dihydroxyphenylethylene glycol.[46] Thus, rather than being due to increased secretion, the increase may be due to decreased metabolism or clearance of norepinephrine by the ingestion of alcohol. Potter et al, however, did not find any significant increase in plasma epinephrine nor epinephrine after acute alcohol ingestion.[47]

Withdrawal phenomenon

Acute alcohol withdrawal in heavy drinkers during detoxification has been found to be associated with an elevation of blood pressure and tachycardia which was related to the severity of withdrawal symptoms.[13]

In the Lipid Research Clinics Prevalence

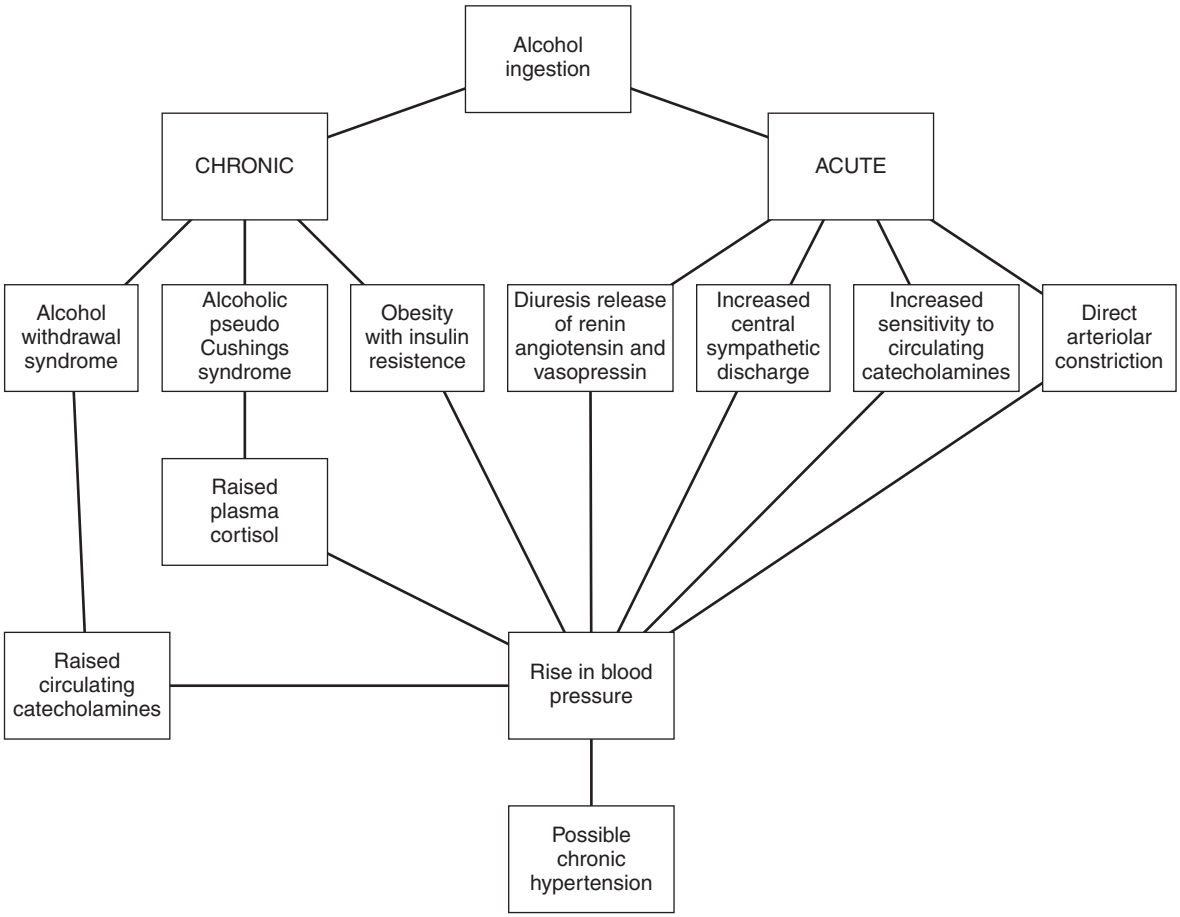

Figure 5.3
Candidate mechanisms for the relation between alcohol and hypertension.

Study, blood pressure was more closely related to alcohol consumption in the previous 24 hours than to total alcohol consumed in the previous week.[33] These findings have led to the suggestion that hypertension related to alcohol consumption may be due to intermittent withdrawal states occurring between drinks. The INTERSALT study findings support this idea, since amongst heavy drinkers with a low variability of alcohol intake, there was a small non-significant mean blood pressure difference in comparison to non-drinkers.[7] Drinkers with high variability in alcohol consumption however had significantly higher blood pressures than non-drinkers.

In the interventional studies by Puddey et

al, the fall in blood pressure was gradual and not associated with withdrawal symptoms.[16] This hypothesis therefore remains to be proven. Potter and Beevers found that, after cessation of alcohol consumption there was an immediate (within 24 hours) fall in blood pressure without an initial elevation.[14] Seppa et al found that, in a group of 20 moderate drinkers who were asked to consume 2.2 g/kg of alcohol in 6 hours, the blood pressure was 5 mmHg higher during the intoxicated period than during the sober period or the 'hangover' period.[48] The blood pressure fell as the blood alcohol level fell, which suggests a direct pressor effect of alcohol rather than the blood pressure changes being due to withdrawal.

Cortisol and the renin/angiotensin system

Potter et al found that plasma cortisol, but not renin, increased during alcohol consumption in hypertensive heavy drinkers and fell during the abstinence phase.[47] Alcohol can thus induce a state similar to Cushing's syndrome. The elevations in blood pressure related to alcohol may therefore in part be due to raised total body water as a result of excessive cortisol and mineralocorticoid production. Arkwright et al found, by contrast, that drinkers had higher blood pressures than non-drinkers but both groups had similar levels of plasma epinephrine, norepinephrine, cortisol, aldosterone and renin levels.[49]

Increased vascular sensitivity

Altura found that the administration of alcohol to rats resulted in an increase in the vascular responsiveness of certain arterioles to locally administered catecholamines.[50] An increased vascular responsiveness may perhaps be mediated by changes in calcium transport in vascular smooth muscle. Indeed, Arkwright et al found a correlation between diastolic blood pressure and plasma calcium in drinkers.[51]

Also in keeping with these observations, Potter et al found that after alcohol consumption, there is a fall in mean plasma calcium levels.[47] This may perhaps be due to a rise in intracellular calcium, which could facilitate vasoconstriction. The rise in intracellular calcium may be mediated via changes in sodium transport[52] or occur as a result of magnesium depletion.[49,50]

Endothelial dysfunction

The relationship between hypertension and endothelial dysfunction has been studied increasingly, and the effects of alcohol on blood pressure could perhaps be mediated via the endothelium. For example, the study by Criscione et al suggested that alcohol suppressed endothelium-dependent vasorelaxation in rat mesenteric vascular beds resulted in increased vasoconstriction in response to norepinephrine.[53]

However, when a plasma marker of endothelial damage or dysfunction, such as von Willebrand factor (vWf)[54] is measured on a population-basis, such as in the Atherosclerosis Risk in Communities (ARIC) Study,[55] an inverse relationship between vWf and ethanol consumption was observed.

Alcohol and cardiovascular disease

Little doubt remains that alcohol consumption is associated with an increase in blood pressure. However, there is little evidence that alcohol is associated with coronary artery disease, the main complication of hyperten-

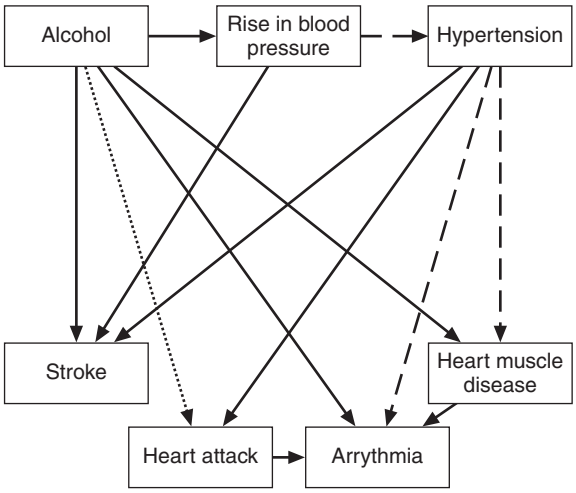

Figure 5.4
The relationship between alcohol intake and cardiovascular disease. Continuous line: known association; broken line; possible association; dotted line; no convincing or inverse association.

sion, although there may be an association with strokes. There is even some evidence that alcohol may afford some protection against coronary artery disease. Alcohol is, however, strongly associated with cardiac arrhythmias and heart muscle disease (Fig. 5.4).

Ischemic heart disease

Many studies have examined the relationship between ischemic heart disease and alcohol intake and most have found a lower incidence amongst drinkers.

Rimm et al found an inverse relationship between alcohol intake and coronary artery disease in a prospective study of 51 529 male health professionals, which persisted after adjustment for other coronary risk factors.[56] All-cause mortality was reduced in mild to moderate drinkers and the increase in mortality in heavy drinkers (>34 g/day of alcohol) was due to non-cardiac causes.

In the Kaiser-Permanente study, a prospective study of 120 000 people in the San Francisco area, those who took two or fewer drinks a day were least likely to require hospitalization during the follow-up period, while those who took six or more drinks a day were the most likely group to require hospitalization (49.3% vs 53.2%).[57] When the causes for admission were analysed, it was found that hospitalization rates for all coronary disease were substantially higher in non-drinkers (8% vs 5.6%) than in heavy drinkers. In addition, amongst the subjects admitted to hospital with a myocardial infarction, there was an excess of abstainers from alcohol. However, hypertension was not controlled for and, as the authors pointed out, heavy drinkers are usually more likely to be heavy smokers. Thus, the inverse relationship between alcohol and coronary artery disease may be even stronger than suggested. The relationship between alcohol and heart disease in women is a less clear-cut possibility because a heavy alcohol intake is less common in women. Nevertheless, a protective effect of moderate intake has been reported in women.[58]

The Honolulu Heart Study found a similar inverse relationship between the amount of alcohol consumed and the incidence of coronary heart disease, even when confounders (including age, blood pressure, cholesterol, weight and cigarette smoking) were taken into account.[59] Alcohol intake was nevertheless positively related to the risk of death from cancer and hemorrhagic stroke. Doll et al also reported a prospective study of 12 321 British male doctors and found that the consumption

of alcohol seemed to reduce the risk of ischemic heart disease.[60] In addition, Kozararevic studied 11 121 Yugoslavian men and found that those who drank less often than once a day had a higher incidence of CHD than those who drank daily.[61]

In an angiographic study of people who presented to hospital with chest pain, Handa et al found significantly less atherosclerotic occlusive disease in heavy drinkers.[62] Barboriak also found that the extent of coronary artery occlusion was inversely related to the amount of alcohol intake in men and women.[63]

In the Department of Health Hypertension Care Computing Project, Palmer et al looked at the relationship in a group of 6369 hypertensive subjects and found that the lowest risk of ischemic heart disease mortality occurred at an alcohol intake rate of >21 units per week, with a relative risk of 0.65 ($p = 0.03$).[64] The risk of death from non-circulatory causes tended to increase with greater alcohol consumption, and men who drank >21 units of alcohol per week had a two-fold higher risk. By contrast, the British Regional Heart Study did not find any significant relationship between alcohol and CHD, although the pressor effect of alcohol offset any benefits, such as the rise in HDL-cholesterol.[65]

It has been suggested that the beneficial effect of alcohol on lipids and lipoproteins may be responsible for any protective effect of moderate alcohol consumption. Alcohol intake increases the protective HDL-cholesterol levels whilst decreasing LDL-cholesterol.[66] Alcohol also seems to reduce plasma fibrinogen, of which high levels have adverse prognostic implications, and inhibit platelet activity.[67,68] Other studies have suggested that anti-oxidants in red wine are responsible for the inverse relationship seen.[69] However the studies by Palmer et al[64] and by Kozararevic et al[61] did not clearly show that any particular type of drink was more beneficial.

Not all studies, however, have shown that alcohol had a 'protective' effect against heart disease. A Swedish study of alcohol-discordant twins found no difference in the incidence of ischemic heart disease related to alcohol use.[70]

Cardiac arrhythmias

Cardiac arrhythmias, especially supraventricular arrhythmias, seem to occur much more commonly in heavy drinkers, particularly after episodes of heavy consumption. Such observations have led to the term 'holiday heart' syndrome, referring to acute disturbances of cardiac rhythm with heavy alcohol consumption in people with 'normal' hearts.[71,72] The study by Ettinger et al described 32 episodes of atrial arrhythmias in 24 chronic heavy alcohol users, which mainly occurred during the holiday season.[71] Lowenstein et al reported that, in patients below 65 years of age with new onset atrial fibrillation, alcohol caused or contributed to the arrhythmia in 63% of cases.[72] In a survey of two UK general practices, however, alcohol-related atrial fibrillation was found in 5.4%.[73] The mechanisms for alcohol-related atrial fibrillation may be related to increases in levels of catecholamines, the direct toxic effect of alcohol exerted by acetaldehyde on the myocardium and changes in conduction and refractory times.[74] Alcohol may also cause arrhythmogenic changes in serum electrolyte concentrations. Acute alcohol ingestion can influence the parasympathetic system, especially with vomiting; such vagal stimulation can provoke atrial arrhythmias.[74]

Recent consumption of large quantities of alcohol has been implicated in the etiology of some sudden cardiac deaths, which are usually considered to be arrhythmic in origin. In a series of 100 sudden deaths, 18% were associated with a large consumption of alcohol in the hours preceding death.[75] In a prospective study of 7735 middle-aged British men followed up for 8 years, Wannamethee and Sharper noted that the incidence of sudden cardiac death was highest (nearly a two-fold increase) in heavy drinkers, that is, those consuming more than six drinks per day (>336 g of alcohol per week).[76] However, this was not found in the Kaiser-Permanente study.[57]

Sudden death in these studies may be related to ventricular arrhythmias. For example, one study of intoxicated chronic alcoholics found that ventricular premature depolarizations occurred in 39%.[77] High-speed ECG studies have also demonstrated conduction delays in habitual drinkers who have no other clinical evidence of heart disease.[71]

Heart failure and alcoholic heart muscle disease

It has long been recognized that there is a link between cardiac dysfunction and alcoholism. In 1906, Steell noted the association of alcoholic heart disease to the malnutritional state of beri-beri.[78]

Alcoholic patients have been found to have abnormally high left ventricular end-diastolic pressures and reduced cardiac contractility, even in the absence of overt heart failure.[79] This led to the popular term 'alcoholic cardiomyopathy', although the term 'cardiomyopathy' should now be reserved for idiopathic heart muscle disease, rather than that due to secondary causes such as alcohol.

The evidence that alcohol is associated with heart failure is convincing. For example, Olubodun found that, in a group of hypertensive patients, heavy alcohol consumption appeared to be a major contributing factor to heart failure.[80] Alcohol is also associated with hypertension, which in turn is related to coronary artery disease. In addition, alcohol is a precipitant of atrial fibrillation which is frequently associated with both heart failure and coronary artery disease.[81]

The precise pathophysiologic mechanisms of alcohol-related cardiac failure still remain to be elucidated. Nevertheless, postmortem findings have shown some degree of interstitial fibrosis in alcoholics.[82] It is also recognized that the first metabolite of alcohol, acetaldehyde, can significantly impair myocardial contractility. Deficiencies of certain nutrients, such as thiamine, may also play a role, as may toxins in the beverages, such as lead[83] or cobalt.[84]

In the Framingham study, alcohol use was associated with left ventricular mass independently of blood pressure,[85] as it was in two Italian studies of hypertensives.[86,87] In the study of hypertensive patients by Melina et al, left ventricular mass was significantly higher in alcoholics than in non-alcoholics.[86] Vriz et al studied 793 males with borderline to mild hypertension and found that left ventricular mass index, interventricular septum thickness and wall thickness increased with increased alcohol consumption, even after adjustment for smoking and 24 hour blood pressure.[87]

Stroke

Since alcohol predisposes to hypertension, and hypertension predisposes to stroke, one would expect there to be a relationship between alcohol and stroke.

Perhaps the earliest documented cerebrovascular casualty of excessive alcohol consumption was that of Nabal: '... On her return she found Nabal holding a banquet in his house, a banquet fit for a king. He grew merry and became very drunk, so drunk that his wife said nothing to him, trivial or serious, until day-break. In the morning she told him everything, and he had a seizure and lay there like stone. Ten days later the Lord struck him again and he died.' (1 Sam, 25: 36–38. New English Bible.)

The nature of the relationship between alcohol and stroke remains far from clear. For example, You et al found that the relative risk of stroke in the under-55 age group was increased 15-fold in those with longterm, heavy alcohol use.[88] In an elderly Taiwanese population, alcohol consumption of over 367.6 g per week was associated with a high prevalence of stroke, although this relationship was lost after adjustment for other confounders.[89]

By contrast, the Yugoslavian Cardiovascular Disease Study by Kozararevic et al found that the association between alcohol consumption and stroke was lost if systolic blood pressure was included in the multivariate analysis.[61] The Kaiser-Permanente study found an increasing trend in the incidence of stroke with increased alcohol use, although this difference was not statistically significant because of the small numbers involved.[57] In the Honolulu Heart Study there was no relationship found between alcohol use and cerebral infarction, but a significant relationship with cerebral hemorrhage was present.[59] The Department of Health Hypertension Care Computing Project prospectively studied 6369 hypertensive subjects and found that the incidence of stroke in their population was significantly lower in male drinkers than non-drinkers (relative risk 0.57) and that the risk was lowest in wine drinkers (0.34).[64]

In Japan, Kiyohara et al followed 1621 stroke-free subjects aged >40 years for 26 years.[90] They found that, among hypertensive subjects, light alcohol consumption reduced the risk of cerebral infarction, but the incidences of cerebral hemorrhage and infarction were significantly increased in heavy drinkers. The link between alcohol and cerebral hemorrhage was also seen in a Finnish study designed to identify modifiable risk factors for spontaneous intra-cerebral hemorrhage (relative risk 11.3 if >120 g of alcohol drunk in the preceding 24 hours, 6.5 if >300 g drunk in the preceding week).[91] A case-controlled study of stroke patients reported by Gill et al in the UK found an increased relative risk of stroke in people who consumed more than 4 units per day.[92] This effect was seen for both cerebral hemorrhages as well as cerebral infarcts, even after adjusting for confounding variables.[92]

Thus, there may be an association between alcohol intake and stroke but this is still not absolutely certain. The contribution of hypertension must also be taken into account.

Implications for public health

Mathews et al suggested that if the relationship between alcohol consumption and blood pressure is linear, 10–20% of hypertension could be due to alcohol consumption in countries with a *per capita* consumption similar to that in Australia, which is approximately 10 litres of absolute alcohol annually.[93] This figure is likely to be lower in women because

of their lower level of alcohol consumption. Beilin et al estimated that the consumption of at least three drinks per day would result in a 3–4 mmHg increase in systolic blood pressure and a 1–2 mmHg increase in diastolic blood pressure.[94]

Alcohol also appears to make the control of hypertension more difficult. If this is true, a reduction in alcohol consumption could result in a substantial fall in the prevalence of hypertension. However, Stamler et al found that long-term compliance with low alcohol regimes was generally poor.[95] Long-term, randomized, controlled trials are therefore needed to determine the true value of reducing alcohol consumption on blood pressure.

Although alcohol may be associated with a lower risk of stroke or ischemic heart disease, many of the studies found that hospitalization for all causes and all-cause mortality was greater in heavy drinkers.[57] Thus, in the Yugoslavian Cardiovascular Disease study,[61] deaths from cancer, cirrhosis and accidents and violence were significantly increased with alcohol consumption. Similarly, in the Department of Health Hypertension Care Computing Project,[64] men who drank >21 units of alcohol a week had a 2-fold increased risk of non-cardiac death. A higher all-cause mortality was also seen in heavy drinkers in the Chicago Peoples' Gas Company and the Chicago Western Electric Company studies.[9] In the Honolulu Heart Study, however, there was a J-shaped relationship between all-cause mortality and alcohol consumption, with an excess of deaths in heavy-drinkers and a slight increase in non-drinkers.[59]

Conclusion

There is now substantial evidence that alcohol has a causal relationship to hypertension and cardiovascular disease. This has significant cost implications as well as mortality and morbidity sequelae. When advising patients about alcohol consumption, it is important to take each individual's characteristics into consideration. There will be a number of people who should be advised to abstain completely, especially those who are problem drinkers and people who already manifest alcohol-related pathologies. Other patients, such as those with congestive cardiac failure or cardiac arrhythmias should be advised to drink sparingly. People with hypertension and possibly angina should also be advised to drink in moderation only.

The common recommendation is that men should consume no more than 21 units/week, and women no more than 14 units/week. This seems sensible, for if alcohol does cause hypertension and stroke, it tends to do so at greater than 2–4 drinks per day, and below that level there may even be some cardiovascular protective effect. Alcohol consumption may be a common feature in everyday life of our population, but it is only recently that we are beginning to appreciate the complex relationship alcohol has with cardiovascular disease and risk factors.

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6

Diabetes and the Heart

James Lawrence and John PD Reckless

Introduction

Diabetes mellitus is increasingly common. Worldwide it is predicted that the numbers of people with diabetes will double over the next 15 years.[1] In the UK, it is found in at least 2% of the Caucasian population[2,3] and in up to 20% of some ethnic minority groups. With the same number of patients undiagnosed at any one time,[4,5] it is clear that diabetes and its management is to place an increasing burden on health care systems around the world. In the UK, diabetes currently consumes at least 9% of healthcare expenditure, with much of this being used to treat complications. In the US, over $100 billion is spent annually on diabetes. For many years the main focus of management has been directed firstly towards symptomatic control and secondly towards recognizing and treating diabetes-specific complications, particularly retinopathy, neuropathy and nephropathy. There is no doubt that interventions to reduce the incidence and impact of these complications are partially effective in both type 1 and type 2 diabetes.[6–9] However, it is clear that cardiovascular disease, and particularly coronary heart disease (CHD), greatly limits the expectation and quality of life of patients with diabetes. These patients have not seen the same fall in cardiovascular mortality seen in the general population.[10]

Population-based studies have suggested that, with diabetes, the relative risk of dying of CHD is 2–3 times that of the general population in men and 3–5 times that of the general population in women.[11–17] The absolute risk in women is approximately the same as in men. Eighty percent of patients with diabetes will die of cardiovascular disease, with at least 50% dying of CHD. Cardiovascular disease alone is largely responsible for the reduction of life expectancy of approximately 30% at any age of diagnosis of diabetes.[18] Patients with diabetes have a consistently poorer survival after a myocardial infarction (MI). Mortality is increased in-hospital, at 1 month, at 1 year and at 5 years,[19–21] and may be as high as 70% at 5 years (compared to 23–50% in those without diabetes).[22,23] These patients also have a much higher rate of reinfarction.[22,24]

In addition to increased CHD risk, patients with diabetes have a significantly increased stroke risk, with a two- to four-fold excess risk of death from cerebrovascular disease (CVD).[25] Peripheral vascular disease is also more common. Claudication is seen four times more commonly in men with diabetes and six times more commonly in women with diabetes.[11,26] Gangrene is 60 times more common than in the general population.[27]

Diabetes and macrovascular disease

Undoubtedly, the classical risk factors of hypertension, hyperlipidemia and smoking increase the risk of macrovascular disease in diabetes.[28] These often cluster together and the presence of multiple risk factors in one patient explains some, but certainly not all, of the excess macrovascular risk.

Blood pressure

Hypertension is twice as common in patients with diabetes, and is seen in 10–30% of patients with type 1 diabetes, particularly in association with nephropathy.[29] Blood pressure usually starts to rise in the early stages of nephropathy, when the albumin excretion rate exceeds 30 mg/24 hours (microalbuminuria). By the time proteinuria is dip-stick positive (albumin excretion rate >300 mg/24 hours), patients are often hypertensive.[30] Blood pressures of <140/<90 may represent relative hypertension in youngsters.[31,32]

Hypertension is more common in type 2 diabetes than in the general population, and affects 30–50% of patients overall and 65% of patients with diabetes duration >30 years.[29,33] This high rate of hypertension in type 2 diabetes may also be linked to insulin resistance and hyperinsulinemia. Insulin causes retention of sodium and water by direct action on the distal renal tubule and may also stimulate Na^+-K^+_{ATP} in cell membranes. Together, these effects increase intracellular sodium, may increase intracellular calcium in vascular smooth muscle and result in increased contractility and raised vascular resistance. Insulin also may increase proliferation of vascular smooth muscle, which could lead to hypertrophy of the arterial media and increased peripheral vascular resistance. It may act as an endothelial vasodilator, an action which may be reduced in insulin-resistant states with the resulting increase in vascular tone.[29]

Blood pressure usually shows a circadian rhythm with a fall in systolic and diastolic blood pressure during the night. This 'dipping' may be lost in patients with diabetes. This can be seen early in the course of type 1 diabetes.[34] It is particularly common in patients with nephropathy, where it is associated with deterioration of renal function and also increased mortality.[35,36] The role of 24-hour blood pressure monitoring has yet to be clearly defined in diabetes, and whether identifying and treating 'non-dippers' more actively will improve outcome is also unclear but is certainly an area for further research.

Lipids and lipoproteins

Although the relationship between cholesterol and risk of cardiovascular disease is similar in diabetes as it is in the general population,[28] patients with diabetes typically do not have an especially raised total- or low density lipoprotein (LDL)-cholesterol.[27] In type 2 diabetes, patients often have raised triglycerides in association with a low concentration of high density lipoprotein (HDL) cholesterol.[37,38] Undoubtedly a low HDL-cholesterol is associated with increased risk of CHD. High triglycerides are a powerful univariate risk factor for CHD.[39–42] In multivariate analysis, particularly when correcting for HDL cholesterol, this effect is less marked, but a recent meta-analysis suggested that triglycerides remain an independent risk factor.[43] The triglyceride-HDL changes in type 2 diabetes are more marked in women than in men, which may be

part of the explanation for the greater change in risk for women with diabetes than for men with diabetes compared with the general population. In type 1 diabetes, HDL-cholesterol levels may be normal or high, but do not necessarily protect fully against CHD.

The characteristic 'diabetic dyslipidemia' reflects multiple changes in metabolism of lipids and lipoproteins which can explain some of the increased CHD risk (Fig. 6.1). In type 2 diabetes, as a consequence of insulin resistance, suppression of lipolysis in adipose tissue by insulin is reduced, with a resulting increase in the plasma concentration of non-esterified fatty acids and increased flux to the liver.[44,45] Hepatic triglyceride synthesis is thus

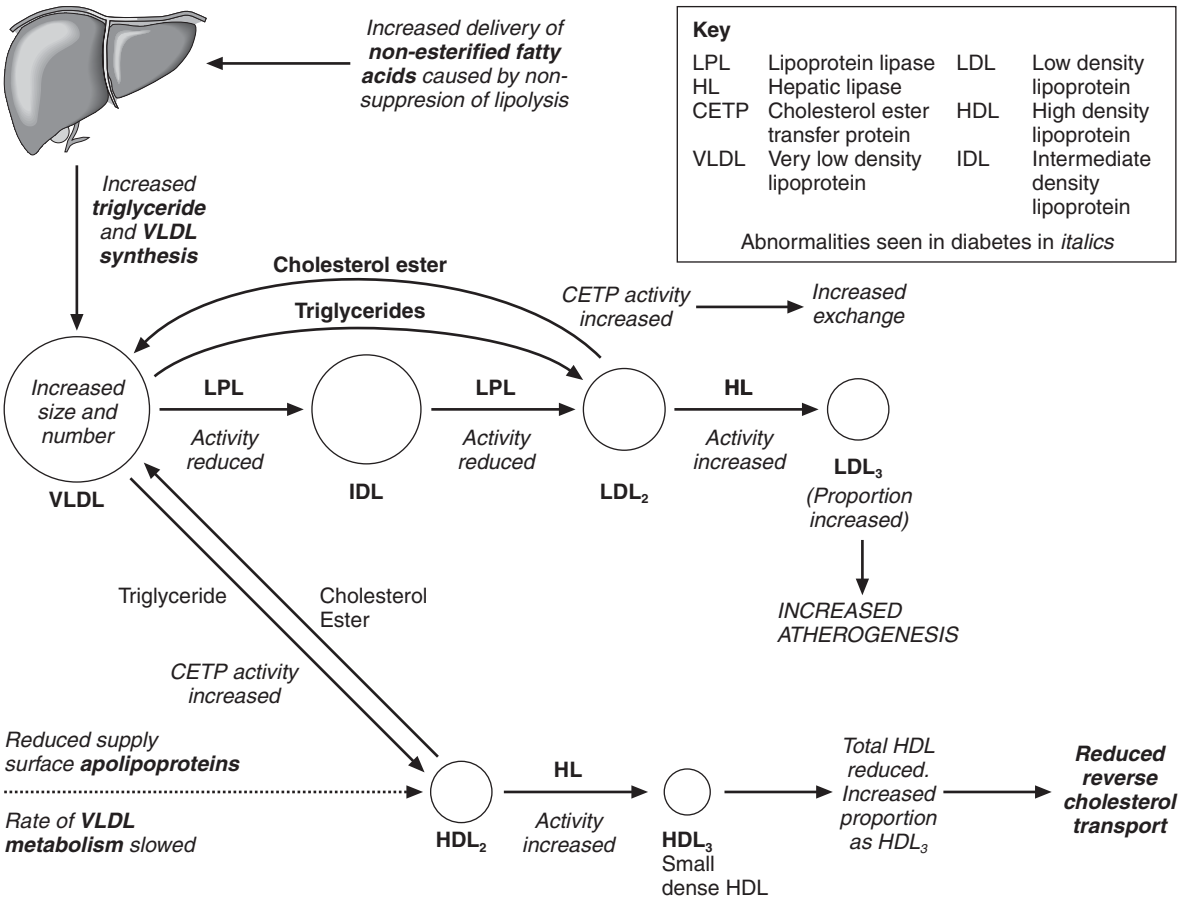

Figure 6.1
Lipoprotein metabolism in diabetes.

increased, the triglyceride being packaged into very low density lipoprotein (VLDL) particles and secreted into the blood stream. The increased triglyceride synthesis results in secretion of an increased number of triglyceride-enriched, and hence larger than normal, VLDL particles.

In the periphery, VLDL is converted to LDL. This depends on the activity of the enzyme lipoprotein lipase which hydrolyzes the triglycerides in VLDL. This enzyme is insulin sensitive and its activity is reduced in insulin resistant states.[46,47] In addition the larger, triglyceride-laden VLDL particles seen in diabetes are a less good substrate for the enzyme.[48] Slower VLDL catabolism leads to increased residency time of VLDL in the blood, and therefore to an increase in the continuous exchange of triglycerides and cholesterol ester between VLDL and both HDL and LDL catalyzed by the enzyme cholesterol ester transfer protein. The net effect is to produce VLDL containing increased cholesterol ester and HDL/LDL particles containing increased triglyceride.

This LDL and HDL-triglyceride is hydrolysed by the enzyme hepatic lipase. As triglyceride is removed, HDL and LDL particles become smaller and denser. The small, dense HDL particles are more rapidly removed from the circulation and are also less efficient in reverse cholesterol transport, a crucial protective mechanism against atheroma formation.[49] The small, dense LDL particles (LDL_3) are less efficiently bound by the normal LDL receptor.[50] Longer plasma residency time increases the chance of modification by glycation and of entry into the subendothelial space. LDL_3 is more prone to oxidative modification, particularly if glycated.[51–53] Modified LDL is more efficiently taken up by scavenger macrophages in the arterial sub-intimal space[54] and thus may be more potent in promoting atheroma formation.

Postprandial lipoprotein metabolism is also abnormal in type 2 diabetes. Usually VLDL synthesis is inhibited by insulin action in the fed state. This is less marked in type 2 diabetes[55] and as a result post-prandially patients often have not only chylomicrons but also increased VLDL in the circulation. These are both metabolized by lipoprotein lipase, the action of which is already suppressed in the insulin resistant state. Not surprisingly, metabolism of chylomicrons and VLDL is slowed and increased chylomicron and VLDL remnants are seen in the blood. This process not only promotes formation of small, dense LDL and HDL but these remnants may be directly atherogenic and contribute to the increased risk of macrovascular disease.[48,56–58]

In type 1 diabetes, similar lipid abnormalities are seen when diabetes is poorly controlled, but these are largely corrected if control is improved. In type 2 diabetes, improved control may only partially correct the multiple abnormalities in lipid and lipoprotein metabolism.

Glucose

Diabetes is an independent risk factor for cardiovascular disease, although the association between the level of glycemic control and increasing cardiovascular risk is less clear than that between glycemic control and microvascular complications. The glucose threshold for diagnosing diabetes is based on the risk of developing microvascular complications. It is not surprising that the same threshold effect is not seen for macrovascular disease. Patients with lesser degrees of glucose intolerance are

also at increased risk. Some of this relates to the clustering of risk factors as already described but it seems that glucose at levels below that necessary to diagnose diabetes may be an independent risk factor for CHD. In the DECODE study, patients with impaired glucose tolerance had an increased mortality, with a relative risk of 1.5.[59] Similar results have been seen in a number of other studies.[60,61] Longterm follow up of the Whitehall Study, Helsinki Policemen's Study and Paris Prospective Study has suggested that a fasting blood glucose in the upper 2.5% and a 2-hour post load glucose in the upper 20% of the normal range predict risk of death at 20 years.[62] There is some evidence that post-prandial glucose excursions are particularly associated with increase CVD risk.[63]

Other risk factors

Reaven coined the term 'syndrome X' (also known as insulin resistance syndrome or Reaven's syndrome) to describe the association of insulin resistance, glucose intolerance, dyslipidemia, centripetal obesity, raised uric acid and hypertension.[64] The syndrome has now been extended to include abnormalities in clotting and fibrinolysis which are frequently seen and may increase the risk of macrovascular disease. Raised fibrinogen levels have been shown to be associated with cardiovascular disease both in patients with and without diabetes.[65–67] There seems to be a relationship between fibrinogen levels and hyperglycemia and, at least in some studies, fibrinogen levels improve with improvement in metabolic control.[68] Plasminogen activator inhibitor-1 (PAI-1) plays a pivotal role in inhibiting fibrinolysis. Levels of PAI-1 are frequently raised in patients with type 2 diabetes[69] and may be raised in patients with a MI, both with and without diabetes.[70,71] Raised levels may also be associated with an increased risk of re-infarction.[72] Whether either raised PAI-1 or raised fibrinogen is causally related to the increase in cardiovascular disease, merely serves as a risk marker, or is raised as a consequence of atheroma, either overt or occult, is unclear.

Atheroma in diabetes[73,74]

Atheroma occurs in large elastic and muscular arteries, such as the aorta, coronary, femoral and carotid arteries and especially at predisposed sites such as vessel bifurcations where there is disturbance in laminar blood flow. The initiating event in atherogenesis seems to be endothelial injury, which produces a number of changes pivotal to atheroma formation:

- Increased ingress of LDL into the subintimal space where it is modified.
- Increased expression of adhesion molecules which bind circulating monocytes. These migrate into the subintimal space, are immobilized and are transformed to macrophages. After expression of scavenger receptors, these take up modified LDL to form foam cells.
- Increased synthesis of multiple cytokines by endothelial cells and activated macrophages. These are involved in a complex series of steps resulting in migration and proliferation of smooth muscle cells which synthesize a connective tissue matrix rich in collagen, elastin and proteoglycans.

The atheromatous plaque is made up of a lipid rich core with an overlying fibrous cap.

Rupture of the plaque may result in acute vessel occlusion. This is most likely to occur where the plaque is thinnest, at the shoulder, and is precipitated by the production of metalloproteinases by macrophages. The greater the degree of inflammation in the vessel wall, and the higher the LDL concentration, the greater the number of foam cells. The synthesis of metalloproteinases will be increased in this situation with a resultant increased chance of plaque rupture.

Histologically atheromatous lesions in diabetes are the same as in other patients but tend to be more extensive and run a more aggressive course. A number of factors may contribute to this. Hypertension is more common, increases sheer stress, and promotes endothelial dysfunction. Acute hyperglycemia also leads to endothelial dysfunction, as does the formation of advanced glycation end products in the longer term.[75,76] Small dense LDL may promote atherogenesis as described previously.

Management of lipids in diabetes

Many trials have studied management of hyperlipidemia in both primary and secondary prevention of CHD, but none of the large trials have been designed to look specifically at patients with diabetes. Clinical guidelines for suggested management have resulted from diabetic subgroup analysis of the general population in large trials. As in the general population, much of the evidence in diabetes relates to treatment of raised cholesterol using 3-hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins). These may have effects beyond direct lipid lowering in reducing CHD risk, including improvements in endothelial function, anti-inflammatory actions and actions to enhance smooth muscle proliferation, all of which will increase plaque stability.[77] Whether these other effects are truly independent of cholesterol lowering is unclear.[78]

In the United Kingdom, the statin choice is between atorvastatin, cerivastatin, fluvastatin, pravastatin and simvastatin where 10 mg, 400 μg, 60 mg, 40 mg and 20 mg respectively have roughly equal potency, of around a 30% fall in LDL cholesterol.[79] In the US and elsewhere lovastatin is also available, for which the equivalent dose is 40 mg.

Secondary prevention

The Scandinavian Simvastatin Survival Study (4S) and the Cholesterol and Recurrent Event Trial (CARE) both had significant diabetic subgroups (Table 6.1). The 4S study included 202 patients with diabetes with a previous MI or angina, a cholesterol of 5.5–8 mmol/l and triglycerides <2.5 mmol/l.[80] Treatment with simvastatin for a mean of 5.4 years resulted in a fall in total cholesterol of 27%, a fall in LDL of 36%, a fall in triglycerides of 11% and an increase in HDL-cholesterol of 8%. In the simvastatin treated patients compared to placebo, the relative risk was 0.45 for major CHD events (95% CI 0.27–0.74; $p = 0.002$) and 0.63 for any atherosclerotic event (95% CI 0.43–0.92; $p = 0.018$).[80] Similar results were shown in an extended analysis that involved a larger proportion of the initial patient cohort where the 1997 American Diabetes Association criteria were used to diagnose diabetes and impaired fasting glucose (Table 6.1).[81]

The CARE study included 586 patients with diabetes with a previous MI and LDL cholesterol of 3–4.5 mmol/l.[82] Pravastatin

Trial	*Number (%) with diabetes*	*Results in diabetic subgroup* *Relative risk (confidence interval) treatment vs placebo*
4S	202 (4.5%)[1]	Total mortality 0.57 (0.30–1.08; $p = 0.087$) Major CHD events 0.45 (0.27–0.74; $p = 0.002$) Any atherosclerotic event 0.63 (0.43–0.92; $p = 0.018$)
4S	483 (10.9%)[2]	Total mortality 0.79 ($p = 0.34$) Major CHD events 0.58 ($p = 0.001$) Revascularization 0.52 ($p = 0.005$)
CARE	586 (14.1%)[1]	Fatal coronary event/non-fatal MI 0.87 (p = ns) All coronary events 0.75 ($p = 0.05$) Revascularization 0.69 ($p = 0.04$)
LIPID	782 (8.7%)[1]	Death from CHD or non-fatal MI 0.81 (0.59–1.10; p = ns)
VA-HIT	627(24.8%)[1]	Death from CHD/non-fatal MI or stroke 0.76 (0.57–1.00; $p = 0.05$)

[1]By 1985 WHO criteria
[2]By 1997 American Diabetes Association Criteria

Table 6.1
Results of diabetic subgroups in large lipid-lowering trials in secondary prevention of CHD.

(40 mg) compared with placebo over 5 years produced a relative risk of 0.75 ($p = 0.05$) for all coronary events and 0.68 ($p = 0.04$) for revascularization procedures.[81] The results in terms of relative risk reductions in the diabetic and non-diabetic subgroups in both studies were similar (Table 6.2). As patients with diabetes have higher absolute risk they gained greater absolute benefit.

Based on these subgroup analyses, guidelines for treatment of hypercholesterolemia for patients with CHD are the same in patients with and without diabetes. In the UK, the Joint British Recommendations on Prevention of Coronary Heart Disease in Clinical Practice suggest starting statin therapy immediately, along with dietary advice, in those with an MI or unstable angina who have a total cholesterol of ≥6 mmol/l.[83] Those with a cholesterol of 5–6 mmol/l should be given dietary advice and receive statin therapy only if the cholesterol is ≥5 mmol/l on retesting at 6–12 weeks. Those with a cholesterol <5 mmol/l should be given dietary advice and be retested annually. These guidelines may be too conservative. The maximum average reduction in cholesterol achieved by diet in free living individuals is <0.5 mmol/l[84,85] and, without initiation of statin treatment in hospital, less than 25% of patients are on treatment with a statin at 6 months. Furthermore, in the MIRACL trial[86] which used 80 mg atorvastatin or placebo, started 1–4 days post-infarct and continued for 4 months, there was a significant 16% relative risk reduction (2.6% absolute risk reduction) in the combined endpoint of CHD events

Trial	*Entry criteria*	*Treatment*	*Relative risk (confidence interval) treatment vs placebo*
4S	Previous MI or angina Total cholesterol 5.5–8.0 mmol/l	Simvastatin/placebo for mean of 5.4 years	Death 0.70 (0.58–0.85; $p = 0.0003$) Coronary death 0.58 (0.46–0.73) One or more major coronary events 0.66 (0.59–0.75; $p < 0.00001$) Revascularization 0.63 (0.54–0.74; $p < 0.001$)
CARE	Previous MI Total cholesterol < 6.2 mmol/l LDL cholesterol 3.0–4.5 mmol/l	Pravastatin 40 mg or placebo for 5 years	Fatal coronary event/non-fatal MI 0.76 (0.64–0.91; $p = 0.003$) Revascularization 0.73 (0.63–0.85; $p < 0.001$) Stroke 0.69 (0.58–0.97; $p = 0.03$)
LIPID	Previous MI or unstable angina Total cholesterol 4.0–7.0 mmol/l	Pravastatin or placebo for mean of 6.1 years	Death from CHD 0.76 (0.65–0.88; $p < 0.001$) Total mortality 0.78 (0.69–0.87; $p < 0.001$) Revascularization 0.8 (0.78–0.9; $p < 0.001$) Stroke 0.81 (0.66–1.00; $p = 0.048$)
VA-HIT	LDL cholesterol <3.6 mmol/l HDL cholesterol <1.0 mmol/l	Gemfibrozil 1200 mg or placebo for 5 years	Fatal coronary event/non-fatal MI 0.78 (0.65–0.93; $p = 0.006$)

Table 6.2
Large lipid lowering trials in secondary prevention of CHD.

and death in the active treatment arm. The LDL cholesterol fell from a mean of 3.2 mmol/l to 1.9 mmol/l over the trial period. It may be more appropriate to treat all patients with diabetes immediately post-infarct if their cholesterol is >5 mmol/l, aiming to reduce total cholesterol towards 4 mmol/l and LDL cholesterol to ≤ 2.5 mmol/l.

In the US, treatment recommendations for hypercholesterolaemia have been set down in the Second Report of the Expert Panel on the Detection, Evaluation and treatment of High Blood Cholesterol in Adults. Again, the advice for secondary prevention is the same whether or not the patient has diabetes, with a target LDL cholesterol of <100 mg/dl (2.58 mmol/l), with drug therapy being initiated in those not reaching target with diet alone.[87]

As already discussed, the typical patient with diabetes will have a low-normal cholesterol associated with high triglycerides and low HDL. The Veterans' Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) was a trial that compared placebo with 1200 mg gemfibrozil in 2531 men with CHD, LDL cholesterol <3.6 mmol/l and HDL

<1.0 mmol/l, values fairly typical of the diabetic population.[88] After 5 years there was a 24% reduction in the combined outcome of death from CHD, nonfatal MI and stroke, with the same effect seen in diabetics and nondiabetics (see Tables 6.1 and 6.2). The primary aim of treatment in secondary prevention in patients with diabetes remains recognition and treatment of hypercholesterolemia, but this trial suggests that, in those with normal cholesterol and low HDL, treatment with a fibrate to raise HDL cholesterol and to lower triglycerides should be considered.

Primary prevention

As with secondary prevention, the trials of lipid-lowering therapy in primary prevention of CHD have only included small numbers of patients with diabetes but have been generalized for the purposes of guidelines on management. Once again guidelines apply largely to the recognition and treatment of hypercholesterolemia rather than to mixed dyslipidemia. The risk of a first CHD event in type 2 diabetes is close to the risk of a recurrent event in patients without diabetes, and this has led Haffner and colleagues to suggest that these patients should be treated as a secondary prevention group, with the same indications for and targets of treatment.[89] This has not been universally adopted but may become the advice in the forthcoming US National Cholesterol Education Programme (NCEP) guideline revision.

At present, the advice in the UK is that patients with diabetes should have their 10-year absolute risk of CHD calculated using charts such as those that accompany the Joint British Recommendations on Prevention of Coronary Heart disease in Clinical Practice.[83] These, like the New Zealand Guidelines[90] and the Sheffield tables,[91] are based on the Framingham algorithm.[92] The Joint British Charts have the advantage of presenting blood pressure and the cholesterol/HDL ratio as continuous variables. Patients with a 10-year risk greater than 30% should be targeted initially and ultimately patients with a risk >15% should be recognized and treated. At this 15% level, or a little lower, treatment with lipid lowering drugs is cost effective. Once the patient is identified, the treatment algorithm is the same as for secondary prevention. In reality, if patients are treated at the 15% risk level, any patient over 45 with diabetes and one other risk factor will be considered for lipid-lowering therapy and treatment will be almost universal. If patients are not treated until they exceed a 3% per annum risk, up to one half may have had an event before therapy is considered.

In the US, advice regarding cholesterol lowering in primary prevention depends on the number of CHD risk factors present (diabetes, hypertension, smoking, male age >45, female age >55, family history of premature CHD, HDL cholesterol <0.9 mmol/l) rather than absolute CHD risk. The advice for patients with less than 2 risk factors is to consider drug therapy following an adequate trial of diet (at least 6 months) in those with an LDL cholesterol ⩾190 mg/dl (4.9 mmol/l) aiming for a target of ⩽160 mg/dl (4.1 mmol/l). In those with 2 or more CHD risk factors the theshold for considering drug therapy is ⩾160 mmol/l with a target of ⩽130 mmol/l (3.36 mmol/l). As age and diabetes are independent risk factors, the vast majority of patients with type 2 diabetes will fall into the high risk group where the threshold for considering lipid lowering therapy and the targets for treatment are more aggressive.[87]

Although most evidence relates to treatment of hypercholesterolemia in primary prevention, there is some evidence that recognition and treatment of hypertriglyceridemia and the associated reduction in HDL is also important. In the Helsinki Heart Study, treatment with gemfibrozil 600 mg twice daily for 5 years, in men with no history of cardiac disease and a non-HDL cholesterol of >5.2 mmol/l, resulted in a significant reduction in cardiac endpoints (relative risk 0.66; CI 0.47–0.92; $p < 0.02$).[93] The group which benefited the most were those with triglycerides >2.3 mmol/l and total/HDL cholesterol ratio >5 mmol/l, values fairly typical of patients with diabetes.[94] Indeed, in a further post-hoc analysis, the small diabetic sub-group showed at least as good an improvement in outcomes (CHD incidence 3.4% in the gemfibrozil-treated men with diabetes, vs 10.4% in the placebo-treated men) although this difference did not reach formal statistical significance because of the small numbers involved.[95] It is in this group that LDL_3 will be expected to be substantially raised as a percentage of total LDL. While statins lower total LDL, fibrates lead to a shift away from LDL_3 to larger, lighter 'more normal' LDL_1 and LDL_2,[96] which substantially corrects qualitative abnormalities.

Diet,[84,85,97] weight loss and improved glycemic control[98–102] may help to correct abnormalities in triglycerides and HDL cholesterol but may not be totally effective. The target for lowering triglycerides is debated. The proportion of LDL present as small dense LDL falls at triglyceride levels below 1.5 mmol/l and this would seem a sensible target. The choice of drug will be guided by the prevailing lipid abnormality. Where patients have raised total- and LDL-cholesterol with only moderately elevated triglycerides (2–4 mmol/l) a statin would be the drug of first choice. Where the cholesterol is <5 mmol/l, but patients have raised triglycerides, a fibrate would be first choice. On occasions it may be necessary to combine the two classes of drug if targets are not reached with either alone but, although well tolerated, this is currently substantially outside the licensed indications and expert advice should be sought if this combination is being considered. With either group of drugs significant disturbance of liver function or myositis may very rarely occur. In asymptomatic individuals on treatment rises in transaminases up to 3 times, and in creatinine phosphokinase (CPK) up to 10 times, the upper limit of normal may be acceptable.

A number of trials of lipid-lowering therapy specifically looking at patients with diabetes are ongoing, including the Lipids in Diabetes Study (LDS), the Fenofibrate Intervention and Event Lowering in Diabetes Study (FIELD), and the Collaborative Atorvastatin in Diabetes Study (CARDS).[103] These trials should help to clarify whether lowering triglycerides improves longterm outcome, whether lipid lowering in patients with 'normal' cholesterol is worthwhile, whether combination statin/fibrate therapy offers advantage and whether there is a lower threshold below which LDL lowering is not worthwhile. The Diabetes Atherosclerosis Intervention Study (DAIS) has been reported recently.[104] Over an average follow up of 38 months, use of micronized fenofibrate 200 mg per day in patients with type 2 diabetes (n = 418), a mean HbA1c of 7.53% and fairly typical lipid values (total cholesterol 5.57 mmol/l, triglycerides 2.42 mmol/l and HDL 1.01 mmol/l) resulted in a 40% reduction in the progression of angiographically assessed coronary artery disease.

Management of hypertension

In a subgroup with diabetes (583 patients out of 4736) in the Systolic Hypertension in the Elderly Program, treatment for 5 years with chlorthalidone and atenolol or reserpine produced an average fall in blood pressure of 9.8/2.2 mmHg relative to placebo.[105] This resulted in a significant reductions in major cardiovascular events, nonfatal MI, fatal CHD and major CHD events, with trends towards reductions in both stroke and all-cause mortality. Similar results were seen in the Syst-Eur study, where patients were randomized to placebo or to nitrendipine, with the addition of enalapril or hydrochlorthiazide if targets were not reached. An average fall in blood pressure of 10.1/4.5 mmHg for 2 years resulted in a significant fall in total strokes (relative risk 0.58, CI 0.4–0.83; $p = 0.003$), non-fatal stroke (relative risk 0.56, CI 0.37–0.86; $p = 0.007$), all fatal and non-fatal cardiac endpoints (relative risk 0.74, CI 0.47–0.97; $p = 0.03$) and all fatal and non-fatal cardiovascular endpoints (relative risk 0.69, CI 0.55–0.86; $p < 0.001$).[106] In this study, 492 patients (out of 4695) had diabetes and the endpoint reductions were greater in this group than in the study as a whole (stroke risk reduction 0.31, CI 0.11–0.88; $p = 0.02$: all cardiovascular events risk reduction 0.38, CI 0.2–0.81; $p = 0.002$: all cardiac events risk reduction 0.43, CI 0.18–1.06; $p = 0.06$).[107]

Although these studies established that blood pressure lowering in diabetes improves longterm outcomes, they did not establish treatment or targets. These issues have been addressed in the United Kingdom Prospective Diabetes Study (UKPDS) and particularly in the Hypertension Optimal Treatment (HOT) trial.[8,108]

In the UKPDS, 1148 hypertensive patients with type 2 diabetes were randomized into a tight blood pressure control group (receiving captopril or atenolol as the main treatment aiming for a blood pressure <150/85 mmHg) or a less tight control group aiming for blood pressure <180/105 mmHg.[8] The mean blood pressure in the tight control group was 144/82 compared with 154/87 in the less tight control group over a median of 8.4 years' follow-up. This resulted in significant reductions of 24% (CI 8–38%; $p = 0.0046$) in diabetes-related endpoints, 32% in deaths related to diabetes (CI 6–51%; $p = 0.019$), 44% in strokes (CI 11–65%; $p = 0.013$) and 37% in microvascular endpoints (CI 11–56%; $p = 0.0092$), although there was no significant difference in the rate of MI. Whilst the study had captopril and atenolol arms, it was far from sufficiently powered to differentiate between these treatments. Interestingly, approximately one third of patients required three or more anti-hypertensives to achieve what was moderate blood pressure control.[109] It has been estimated that, for each 10 mmHg drop in mean systolic blood pressure, there will be a 12% drop for any diabetes-related complication, a 15% reduction in deaths related to diabetes, an 11% reduction in MI and a 13% fall in microvascular complications.[110]

In the HOT trial, 18 790 patients with hypertension and a diastolic blood pressure of 100–115 mmHg were randomized to three groups, with targets of diastolic blood pressure ≤90, ≤85 or ≤80 mmHg (achieved 85.2, 83.2 and 81.1 mmHg respectively).[108] Felodipine was used first line and therapy was titrated according to a preset algorithm. Half the patients were also randomly assigned to receive aspirin 75 mg/day. In the study as a whole, there were no significant differences in

outcomes in the three blood pressure groups.[106] In the subgroup of 1501 with diabetes, the risk of major cardiovascular events and also mortality were significantly lower in the <80 mmHg target group compared with the <90 mmHg target group (11.9:24.4 events/1000 patient years; $p = 0.005$ and 3.7:11.1 events/1000 patient years; $p = 0.016$ respectively). For major cardiovascular events, the lowest point of risk was at mean achieved pressures of 138.5/82.6 mmHg. For stroke, the corresponding values were 142/<80 mmHg.

The results of these and other trials have been incorporated into guidelines on management of hypertension.[111,112] Treatment thresholds and targets for blood pressure differ slightly in the UK and US guidelines. In the UK the current advice is that patients with diabetes should be treated if they have a blood pressure persistently above 140/90 mmHg with target blood pressure of ≤140/≤80 mmHg. In the US the theshold for treatment in patients with diabetes is 130/85 mmHg with a target of ≤130/≤85 mmHg. Many clinicans aim for ≤130/≤80. The choice of therapy will be guided by the presence of coexisting pathology such as angina and heart failure.[112]

There is evidence in patients with type 1 diabetes and nephropathy that angiotensin-converting enzyme (ACE) inhibitors may slow the rate of deterioration of renal function more than other anti-hypertensives and are often used preferentially. Deleterious metabolic effects have been described with beta-blockers and thiazide diuretics in patients with type 2 diabetes. Beta-blockers have been shown to cause significant increases in triglycerides and a significant fall in HDL-cholesterol, but this has not been reflected in poorer longterm outcomes.[113,114] Similarly, thiazide diuretics have been shown to cause dose-related deterioration in glucose levels.[115] This effect is less marked at doses used in hypertension (e.g. bendrofluazide 1.25 mg or 2.5 mg) and again these drugs seem to be as equally effective as other antihypertensive drugs in the long term. Other hypertensive classes are largely metabolically neutral.

When treating patients with diabetes and hypertension it is important to consider the possibility of autonomic neuropathy and associated postural hypotension. Measuring postural blood pressure is important prior to commencement of, and whilst on, treatment.

Management of hyperglycemia

Whether longterm glycemic control results in reduction in macrovascular disease has been debated for many years. The United Group Diabetes Program (UGDP) followed 1000 patients with type 2 diabetes assigned to different therapies for 3–8 years.[116] The results suggested that improved glucose control by any therapy did not reduce the risk of cardiovascular endpoints, and that cardiovascular mortality was actually increased in those patients treated with tolbutamide. However, there have been many criticisms of the UGDP and the results have been questioned. Attempts were made to address these issues in the UKPDS. In this study, 3867 newly diagnosed patients with type 2 diabetes were randomized to an intensive control group aiming for a fasting blood glucose <6 mmol/l or a less intensive group aiming for patients to be asymptomatic with a fasting plasma glucose <15 mmol/l.[6] In the intensive control group,

	Mean HbA1c		*Relative risk (confidence interval) intensive vs conventional treatment*
	Intensive group	*Conventional group*	
Intensive SU/insulin vs conventional treatment	7.0%	7.9%	Any diabetes-related endpoint 0.88 (0.79–0.99; $p = 0.03$)[1] Diabetes-related death 0.90 (0.73–1.11; $p = 0.34$)[1] All-cause mortality 0.54 (0.80–1.10; $p = 0.44$)[1] Retinal photocoagulation 0.71 (0.53–0.96; $p = 0.003$)[2] MI 0.84 (0.71–1.00; $p = 0.052$)[2]
Intensive metformin vs conventional treatment	7.4%	8.0%	Any diabetes related endpoint 0.68 (0.53–0.87; $p = 0.002$)[1] Diabetes-related death 0.58 (0.37–0.91; $p = 0.017$)[1] All-cause mortality 0.64 (0.45–0.91; $p = 0.01$)[1]

[1]Predefined primary aggregate endpoints
[2]Predefined single secondary endpoints

Table 6.3
Main results from glucose lowering in UKPDS.

patients were primarily treated with either a sulphonylurea (SU) or insulin.

During the follow-up of up to 20 years, with a mean of 4 years, the average HbA1c was 0.9% lower (7.0% vs 7.9%) in the intensively treated group. This resulted in a borderline significant reduction in MI (relative risk 0.84, CI 0.71–1; $p = 0.052$), although this was a secondary endpoint (Table 6.3). There was no evidence of increased mortality in those randomized to an SU and although this does provide some reassurance, the numbers in the study may not have been large enough to give a definitive answer to the question of SU safety, which had been raised in UGDP. From the data presented in the study, it has been calculated on an achieved glycemic control basis that, for each 1% reduction in HbA1c there is a 21% reduction for any diabetes-related endpoint (CI 17–24%; $p < 0.0001$), a 14% reduction in MI (CI 8–21%; $p < 0.0001$) and a 21% reduction for deaths related to diabetes (CI 15–27%; $p < 0.0001$).[117] In a fairly small substudy, a proportion of overweight patients were randomized to metformin in the intensively controlled group.[7] With similar improvement in HbA1c, these patients had a significant

improvement in any diabetes-related endpoint, all-cause mortality and stroke compared to those treated with SU or insulin. Overall, the UKPDS results suggest that control of hyperglycemia is at least of some importance in preventing macrovascular disease, with the degree of control achieved being more important than the therapy used. In obese subjects, metformin may be the drug of choice, although a trend against benefit was seen in a fairly similar sized group of patients given a metformin/SU combination.

Short-term hyperglycemia at the time of a MI, whether or not a patient is known to have diabetes, is associated with increased mortality.[118] Control of the hyperglycemia may improve the long-term outcome. In the DIGAMI study, patients admitted with an MI with a blood glucose >11 mmol/l, whether or not they had previous diabetes, were randomized to receive standard care or to receive an insulin/glucose infusion and subsequently to continue insulin for at least 3 months.[119] At 1 and 3 years, there was a significantly lower mortality in the group assigned to intensive treatment (at 1 year relative risk 0.7; $p = 0.027$, at 3 years relative risk 0.72; $p = 0.01$).[119,120] The reduction in risk was largely confined to those patients perceived to be at lowest risk at the start (age <70, no history of MI or heart failure and no treatment with digitalis) who were not taking insulin and indeed were mostly treated with diet alone. The generalizability of these results is questioned for three reasons: only half of patients who were eligible on the grounds of blood glucose were included, there was a large drop-out rate from the insulin arm and a large number of patients in the non-intensive arm were transferred to insulin therapy. It is also unclear whether it is short-term metabolic correction at the time of the MI or longterm insulin therapy with potentially improved control that is important. Nevertheless, it is appropriate to consider all patients with hyperglycemia at the time of MI for an insulin/dextrose infusion to achieve good metabolic control, and to consider continued use of insulin after discharge from hospital for at least 3 months and preferably to 1 year.

Other aspects of management

Evidence for treatment of patients with diabetes post-MI is largely based on subgroup analyses of trials in the general population. Although many treatments are now established in patients with diabetes, these are still substantially underused, and potential benefits reduced as a result.

Thrombolysis

Fear of precipitating retinal bleeding which may threaten sight has resulted inappropriately in patients with diabetes frequently being denied thrombolysis, but this risk is tiny against the 21% reduction in 35-day mortality demonstrated in a meta-analysis.[121] This relative risk reduction is the same as that seen in patients without diabetes. As the absolute risk of death is greater in patients with diabetes, the absolute benefit of thrombolysis is also greater.[122] Only one case of retinal hemorrhage has been described in a patient with diabetes given thrombolytic therapy, which resulted in a 3-week period of visual deterioration.[123] No significant ocular complications were seen in the 6011 patients included in the GUSTO-1 trial.[124]

Beta-blockers

Beta-blockers have been shown to be effective both immediately post-infarction and in the longer term in patients with and without diabetes. Benefits in patients with diabetes may be even greater than in the general population.[125] Despite this evidence, beta-blockers are frequently underused in this group, because of fears of causing deterioration in glycemic control, or of blunting of counterregulatory responses to hypoglycemia. These effects are exceedingly rare, especially with cardioselective drugs, and should not limit their use.[126] Where no absolute contraindications exist, all patients with diabetes should be given a trial of beta-blockers post-MI.

Use of beta-blockers in chronic stable heart failure is now well established, and it produces significant benefits in terms of mortality. Large clinical trials that contain significant numbers of patients with diabetes have demonstrated this, and there is no reason to believe that this group should not benefit to the same extent as the general population.[127–129] Beta-blockers should be considered in patients with diabetes with New York Heart Association (NYHA) grade II, III or IV heart failure who are stable on combined angiotensin converting enzyme inhibitor and/or diuretic treatment who have no absolute contraindications to therapy. Evidence so far supports any of bisoprolol, slow release metoprolol or carvedilol can be used. Treatment should be started on low dose and gradually titrated up, as tolerated, to the dosages used in the clinical trials.

Aspirin

No trials of aspirin post-MI have been conducted exclusively in patients with diabetes. In a meta-analysis, the mortality reduction in both groups of patients was similar (17% with diabetes, 22% without).[130] The optimal dose in diabetes is uncertain and current UK advice is that this should be the same as in the general population.

Aspirin is used increasingly in primary prevention. In the HOT trial, half of the 18 790 patients were randomized to receive aspirin in addition to their anti-hypertensive medication and half were randomized to receive placebo.[108] Use of aspirin resulted in a 15% reduction in major cardiovascular events (8.9:10.5/1000 patient years; $p = 0.03$) and a 36% reduction in MI (2.3:3.6/1000 patient years; $p = 0.002$), with no differences between patients with or without diabetes. As a result, UK guidelines suggest considering aspirin as primary prevention of CHD in all patients, including those with diabetes, who have a CHD risk >15% over 10 years and no absolute contraindication.[83] In the US, aspirin use as primary prevention in patients with diabetes is suggested in those with type 1 and type 2 diabetes at high CHD risk. This includes those with hypertension, obesity, albuminuria, hypercholesterolaemia (cholesterol >5.2 mmol/l), low HDL cholesterol (<1 mmol/l), hypertriglyceridaemia (>2.8 mmol/l), a family history of CHD and smokers.[131] In patients with low cardiovascular risk, potential benefits of aspirin may be out-weighed by risk of gastro-intestinal hemorrhage or hemorrhagic stroke, and the risk/benefit must be assessed in each patient. In those with uncontrolled hypertension, blood pressure treatment towards target should be instituted prior to starting aspirin.[132,133]

Angiotensin converting enzyme inhibitors

Heart failure is very common in patients with diabetes, especially post-MI and accounts for much of the excess risk of mortality in this group. Many trials have demonstrated the effectiveness of ACE inhibitors in heart failure in the general population. A number of these have contained a significant proportion of patients with diabetes, which allows the results to be generalized.[134–137] ACE inhibitors should be considered in all patients with diabetes with clinical congestive cardiac failure or who have systolic dysfunction (left ventricular ejection fraction <40%).

The use of ACE inhibitors may be extended after the results of the Heart Outcomes Prevention Evaluation Study (HOPE).[138,139] A total of 9297 high risk patients over the age of 55 with evidence of vascular disease or diabetes and one other cardiovascular risk factor (hypertension, elevated total cholesterol, low HDL, smoking or microalbuminuria) were randomly assigned to receive 10 mg ramipril or placebo. Use of ramipril resulted in a significant reduction in the primary endpoint, a composite of MI, stroke or death from cardiovascular causes (relative risk 0.78 ramipril vs placebo; $p < 0.001$). The ramipril group also showed significant reductions in MI (9.9:12.3%, relative risk 0.8; $p < 0.001$), stroke (3.4:4.9%, relative risk 0.68; $p < 0.001$), death from cardiovascular causes (6.1:8.2%, relative risk 0.74; $p < 0.001$), and death from any cause (10.4:12.2%, relative risk 0.84; $p < 0.005$), in addition there were reductions in revascularization procedures, cardiac arrest and heart failure. The benefits seen were significantly greater than that expected from blood pressure lowering alone (3/2 mmHg ramipril group:placebo). Whether these results apply to other ACE inhibitors and to angiotensin II antagonists is unclear, as is the exact mechanism of the effect witnessed.[140]

Coronary revascularization

Longterm survival following revascularization procedures is worse in patients with diabetes relative to the general population, possibly as a consequence of older age, more extensive coronary disease and a greater degree of left ventricular dysfunction at the time of surgery. Which procedure is best to use in these patients remains open. In the Bypass Angioplasty Revascularization Investigation (BARI), the overall 5-year survival following revascularization was lower in the subgroup with diabetes (73.1%:91.3%).[141] Patients with diabetes randomized to coronary artery bypass grafting had significantly better outcomes than those randomized to percutaneous coronary angioplasty (5 year mortality of 19%:35%). Benefit was largely confined to patients who had at least one internal mammary artery graft and particularly to patients who used insulin.[141] This study took place prior to use of intracoronary stents and glycoprotein IIb/IIIa inhibitors at the time of angioplasty, and these may improve the prognosis in patients with diabetes.[142,143]

Conclusion

Patients with diabetes are a group at particular risk of CHD with high mortality. One of the primary aims of diabetes care is to reduce this burden, but current management is falling far short of the ideal. The challenge ahead is to ensure appropriate use of the treatments available and to educate patients to ensure compliance as they are expected to take an increasing number of drugs over prolonged periods.

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7

Inflammation and Infection in Coronary Artery Disease

Joseph Ngeh and Sandeep Gupta

Introduction

Coronary artery disease (CAD) is the commonest cause of death in the developed world, and is ever increasing in developing countries.[1] The burden of disease in terms of mortality, morbidity, and socio-economic hardship is considerable. Traditional risk factors of atherosclerosis such as hypertension, tobacco smoking, diabetes mellitus and hyperlipidaemia have been estimated to account for only about 50% of clinical cases of CAD.[2] A number of potential 'novel' cardiovascular risk factors are emerging: one of which is chronic infection.[3–5]

Historically, the concept that infection could be an aetiological factor in atherosclerosis was proposed as early as 1859 by Virchow,[6] followed by Osler[7] in 1908, Frothingham[8] in 1911 and Ophuls[9] in 1921. Infections (micro-organisms and their products), alone and in conjunction with conventional cardiovascular risk factors (LDL cholesterol, smoking), could act as forceful inflammatory stimuli systemically.[10] These stimuli may drive the production (and lead to a dynamic interplay) of various inflammatory cells, cytokines and acute phase reactants in the circulation and on the vascular wall.[10] Indeed, atherosclerosis is now acknowledged as an inflammatory disease.[11]

Research over the last century has implicated a number of micro-organisms that may serve as the potential link between inflammation and atherosclerosis (Table 7.1).[12] *Cytomegalovirus*, *Helicobacter pylori*, and *Chlamydia pneumoniae* (*C pneumoniae*) are the three main infectious agents most investigated in the context of atherosclerotic vascular disease.[12] In particular, *C pneumoniae* has emerged as the most likely 'culprit' causal microorganism. This chapter will therefore focus on *C pneumoniae* as the representative aetiological factor in the 'infectious' hypothesis of CAD.

Chlamydia pneumoniae

Historical background, biological characteristics and epidemiology

Chlamydia pneumoniae was first described as a cause of acute respiratory tract infection in 1986.[13] It was named TWAR (Taiwan acute respiratory) after the discovery of its previous isolates: TW183 in Taiwan in 1965, and AR39 in Seattle in 1983.[13] In 1989, TWAR was renamed *Chlamydia pneumoniae,* a new species, along with the only other two human pathogens: *Chlamydia trachomatis* and *Chlamydia psittaci*, in the same genus.[14,15]

Chlamydia pneumoniae is a Gram-negative,

Microorganism	*Year and author of publication*
Bacillus typhosus	1889, Gilbert and Lion
Streptococci	1931, Benson et al
Coxsackie B virus	1968, Sohal et al
Adenovirus	1973, Fabricant et al
Mycoplasma gallisepticum	1973, Clyde and Thomas
Marek's disease virus	1978, Fabricant et al
Cytomegalovirus	1987, Petrie et al
Herpes simplex virus	1987, Hajjar et al
Chlamydia pneumoniae	1988, Saikku et al
Measles virus	1990, Csonka et al
Epstein-Barr virus	1993, Straka et al
Human immunodeficiency virus	1993, Paton et al
Helicobacter pylori	1994, Mendall et al
Mycoplasma fermentans	1996, Ong et al
Coxiella burnetti	1999, Lovey et al
Porphyromonas gingivalis	1999, Chiu et al
Streptococcus sanguis	1999, Chiu et al
Actinobacillus actinomycetemcomitans	2000, Haraszthy et al
Bacteroides forsythus	2000, Haraszthy et al
Hepatitis A virus	2000, Zhu et al
Influenza virus	2000, Naghavi et al
Prevotella intermedia	2000, Haraszthy et al

(Adapted and modified from Ngeh J, with permission.)[32]

Table 7.1
Microorganisms implicated to associate infection with atherosclerosis or coronary artery disease

obligatory intracellular bacterium.[16] As with other Gram-negative bacterium, its outer membrane contains lipopolysaccharides (LPS) and heat-shock proteins (HSP).[17,18] Several major outer membrane proteins (MOMP) have also been identified.[17,18] While LPS and HSP are genus-specific to all three *Chlamydia* species, MOMP are species-specific antigens detectable by monoclonal antibodies.[17–19]

In its life cycle, *C pneumoniae* is known to exist in three forms: elememtary body (EB), reticulate body (RB), and persistent body (PB).[17–20] The EB is an infective spore that may attack the host's endothelial cells and be phagocytosed by macrophages in the respiratory tract. The EB may then differentiate into a non-infective RB by binary fission in enlarging vacuoles known as inclusion bodies. The RBs are then transformed into EBs, which are released by cell lysis, initiating another life

cycle. However, the EB may unpredictably transform into a metabolically inactive PB within the cell. This PB may remain dormant for an extended period of time, undetected by the host's immune system and unresponsive to antibiotics.

Chlamydia pneumoniae infection is common world wide.[18] A seroprevalence of 50%–70% is detectable in middle-aged and older adults.[21–25] It causes a wide range of clinical manifestations, but primarily infects the respiratory tract.[26] It is responsible for about 6%–10% of cases of community-acquired pneumonia.[15,27] The infection has an incubation period of around 3–4 weeks.[21,28] In western Europe, epidemics due to *C pneumoniae* occur every four to seven years,[23,29] and most adults have been infected by *C pneumoniae* two to three times during their lifetime.[23]

Chlamydia pneumoniae *and coronary artery disease*

The role of *C pneumoniae* in atherosclerosis is based on five diverse areas of investigations:

1. Seroepidemiological observations
2. Pathological specimen examinations
3. Animal model experiments
4. Molecular biological and immunological research
5. Antibiotic intervention studies.[5,12]

Seroepidemiological studies

In 1988, Saikku and colleagues were the first to observe that serological markers (immunoglobulins) of *C pneumoniae* infection were positively associated with CAD.[30] More than 30 seroepidemiological studies had since been published, demonstrating an association between *C pneumoniae* serological markers (immunoglobulins, immune-complexes), *C pneumoniae* DNA antigens (in circulating monocytes), and various artherosclerotic vascular diseases.[5,12] Most of these seroepidemiological studies have been cross-sectional and case-control studies, and have demonstrated at least a two-fold increased risk of cardiovascular events with elevated serological markers, even after statistical adjustment for potential confounders or conventional cardiovascular risk factors.[3,5,12] In 1999, the first prospective study demonstrating a positive association between *C pneumoniae* IgA and subsequent risk of CAD mortality was reported.[31]

Recently, a number of negative seroepidemiological studies, as well as important meta-analysis, have been reported.[5,12,32] Wald et al reported the largest prospective UK study (involving 21,520 professional men aged 35–64) which demonstrated no important relationship between *C pneumoniae* IgG and IgA, and subsequent mortality from CAD.[33] Furthermore, Danesh et al conducted a meta-analysis of 15 prospective studies which demonstrated only a very weak association (OR = 1.15, 95%CI = 0.97–1.36) between *C pneumoniae* IgG and incident CAD.[34] However, the authors commented that further large prospective studies would be needed to confirm or refute any modest association that may exist between *C pneumoniae* serological markers and CAD.[34]

Although the microimmunofluorescence (MIF) technique employed in almost all the seroepidemiological studies is regarded as the 'gold-standard' in the serological analysis of *C pneumoniae* infection, it requires interpretation by an expert microscopist.[5,12,32] The result of MIF is subjective and its reproducibility

questionable.[5,12,32] The enzyme-linked immunosorbent assay (ELISA) may be a more useful alternative test than the MIF.[5,12,32] It is more objective, and has been shown to correlate well (around 90%) with the MIF test, in terms of sensitivity and specificity.[5,12,32] Its reliability and reproducibility needs further study.

The presence of *C pneumoniae* IgA, IgG, or IgM in the serum generally reflects recurrence/persistence, chronic/past, or acute infection, respectively.[5,12,32] However, the exact roles and reliability of these immunoglobulins acting as surrogate markers of and their temporal relations to the actual underlying infection remain unclear.[5,12,32] An elevated antibody titre may simply reflect antigenic cross-reactivity rather than true underlying *C pneumoniae* infection.[35] Individuals' antibody responses to *C pneumoniae* infection may fluctuate over time or may even be variable due to different infective mode, dose, or history of past exposure.[12,32,36] The extent of *C pneumoniae* found in tissue has been shown to correlate poorly with its serological marker.[37,38] Newer diagnostic technique, such as the detection of *C pneumoniae* DNA by polymerase chain reaction (PCR) in circulating monocytes, may prove to be a more accurate surrogate marker of underlying vascular tissue infection.[39,40]

The lack of standardization in *Chlamydia* serology had made comparison of different seroepidemiological studies difficult, as they have often used different cut-off titres to define serpositivity.[5,12,32] Owing to their inherent limitations in *Chlamydia* serological methods, positive seroepidemiological studies at best may only imply a genuine association rather than a causative link.[12] On the contrary, negative seroepidemiological studies do not disprove a potential causative role of *C pneumoniae* in CAD completely.[12]

Pathological specimen examinations

The detection of *C pneumoniae* at autopsy in atherosclerotic lesions of the coronary arteries, using electron microscopy (EM), was first reported by Shor and colleagues in 1992 (Fig. 7.1).[41,42] More than 30 pathological studies have since demonstrated *C pneumoniae* (DNA, protein, and elementary body) in a wide variety of arterial specimens (coronary, carotid, aorta, femoral, popliteal and occluded bypass grafts). A variety of techniques such as immunocytochemistry (ICC), polymerase chain reaction (PCR) (Fig. 7.2),[43] and electron microscopy (EM) have been used in these studies. The rate of *C pneumoniae* detection was about 60% in atherosclerotic lesions, versus 3% in control arterial tissues.[44] Perhaps of greater relevance, 'live', viable *C pneumoniae* have now been cultured from coronary atherosclerotic specimens.[45,46]

Reflecting its ubiquitous presence, *Chlamydia pneumoniae* has also been found in human non-cardiovascular tissues such as lung, liver, spleen, bone marrow, lymph node, and granulomatous specimens.[37] The mere presence of *C pneumoniae* in atherosclerotic lesions does not necessarily infer a direct pathogenetic role. The 'innocent bystander' hypothesis supports the notion that *C pneumoniae* could merely be carried by circulatory monocytes from the site of infection to remain dormant in atheromatous tissues.[12,37] Jackson et al reported that *C pneumoniae* could be detected from a series of tissues removed from 38 autopsy cases at a rate of 29%–50% in cardiovascular tissues versus 5%–13% in non-cardiovascular tissues, and 9% in 33 granulomatous specimens (Table 7.2).[37] Such findings could be interpreted as refuting the 'innocent bystander' hypothesis.

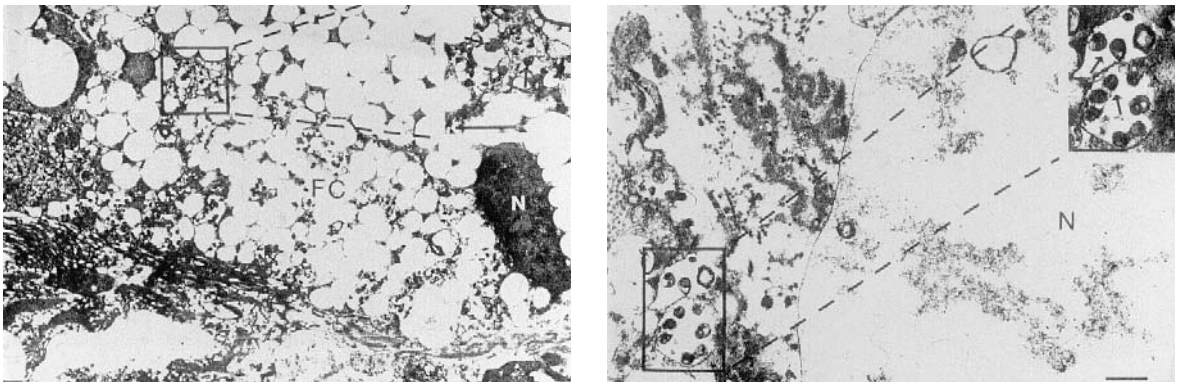

Figure 7.1
Transmission electron micrograph of endosomes in foam cell with elementary bodies of Chlamydia pneumoniae. *Bar = 0.5 µm; FC = foam cell, N = nucleus. Arrows in inset point to elementary bodies. (Reproduced from Kuo CC et al, with permission of University of Chicago Press.)*[42]

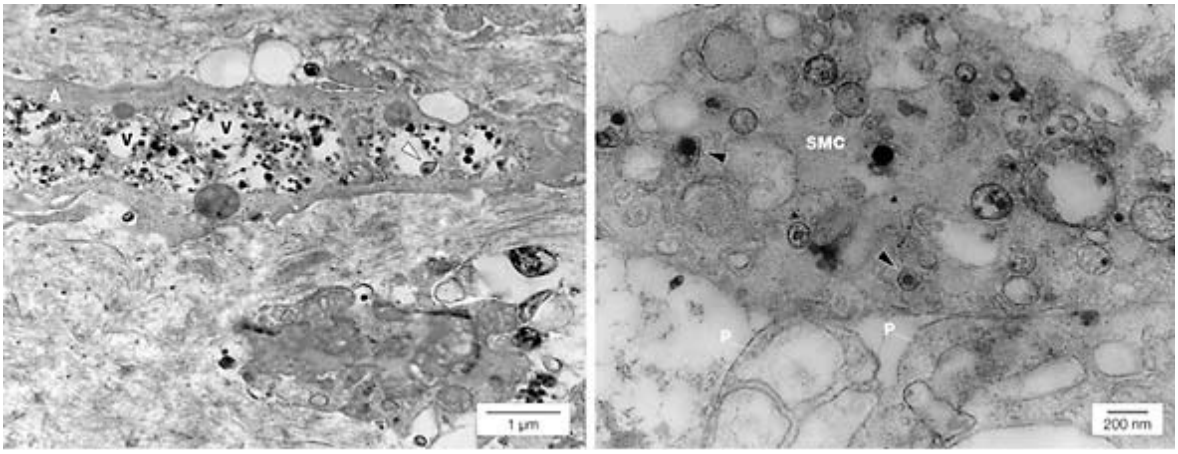

Figure 7.2
Transmission electron micrograph of smooth muscle cells in an early atherosclerotic lesion of the aorta positive for Chlamydia pneumoniae *by polymerase chain reaction.*
On the left, a smooth muscle cell containing vacuoles (V) and Chlamydia pneumoniae *elementary bodies (arrowhead) are demonstrated. The other fragmenting cell and actin (A) filaments are also shown. On the right, macrophage pseudopodia (P) is shown in contact with a fragment of smooth muscle cell (SMC) containing* Chlamydia pneumoniae *(arrowheads). (Reproduced from Shor and Phillips, with permission).*[43]

Tissue	*Number of cases with tissue available for testing*	*Number (%) positive by PCR*	*Number (%) positive by ICC*	*Number (%) positive by ICC and/or PCR*
Cardiovascular				
Coronary artery	38	6(16)	8(21)	13*(34)
Venous bypass graft	2	0	1(50)	1(50)
Myocardium	17	3(18)	2(12)	5(29)
Lung	38	3(8)	2(5)	5(13)
Liver	38	0	4(10)	4(10)
Spleen	38	0	2(5)	2(5)
Bone Marrow	20	2(10)	0	2(10)
Lymph node	12	0	1(8)	1(8)

*One sample positive by both PCR and ICC
(Reproduced from Jackson LA et al with permission).[37]

Table 7.2
Detection rate of C pneumoniae *by PCR and/or ICC in tissues obtained from 38 autopsy cases.*

The EM, ICC and PCR methods used in histopathological studies do not always correlate consistently.[5,12,37] Comparison of these studies among themselves and with seroepidemiological studies is therefore hampered. A standardized histopathological technique may help to resolve this.

Animal models

Historically, animal models of infection-induced atherogenesis include Benson's experiment of *Streptococcus*-rabbit infection in 1931,[47] and Fabricant's experiments of *Herpesvirus*-chicken infection in 1978.[48] More recently, several animal model studies have explored the putative role of *C pneumoniae* in atherogenesis.[49]

Fong and colleagues first reported that 2 out of 11 New Zealand white rabbits infected with *C pneumoniae* developed not only pneumonia, but also fatty streaks and grade III atherosclerotic lesions in the aorta at day 7 and 14 respectively.[50] Another study also demonstrated the development of inflammatory changes, intimal thickening, and fibroelastic plaques resembling atherosclerosis in the aortas of 6 out of 9 rabbits inoculated intranasally with *C pneumoniae*.[51]

Cholesterol supplementation in infected rabbits increases intimal wall thickening, whilst lesion thickness was less marked in

infected rabbits given azithromycin, a macrolide antibiotic active against *C pneumoniae*.[52]

Transgenic mouse models have been critical in exploring interactive or synergistic mechanisms between *C pneumoniae* infection and other atherosclerosis risk factors such as hyperlipidaemia and genetic predisposition. ApoE-deficient mouse developed atherosclerosis in the absence of an atherogenic diet, and repeat *C pneumoniae* infection appears to accelerate lesion progression.[53] In such mice, azithromycin treatment for two weeks did not reduce the size of the aortic lesion.[54] Conversely, the atherogenic effects of *Chlamydia* were dependent on serum cholesterol in a transgenic LDL-receptor-knockout mouse model, and specific to the species *C pneumoniae* rather than *C trachomatis*.[55] In C57BL/6J mice, which do not develop atherosclerosis when fed a normal diet, repeated intranasal inoculation (thereby establishing a persistent infection) with *C pneumoniae* produced intimal thickening, endocarditis and myocarditis.[56,57]

Animal models have shown the pathogenetic role in terms of temporal sequence and infective dose of *C pneumoniae* infection and the subsequent development of atherosclerotic lesions.[12] Genetic predisposition and hyperlipidaemia appear to enhance the atherogenic effect of *C pneumoniae*. Nonetheless, it should be noted that this atherogenic effect is not invariable as *C pneumoniae* is estimated to cause atherosclerotic changes in about 20%–75% of the cases in experimental animal population.[49] Future animal models including primates, may be useful to study the interactions between *C pneumoniae* infection and other well established atherosclerosis risk factors such as hypertension, smoking, and diabetes mellitus. To what extent the pathophysiology and 'acutely-induced' atherosclerosis in laboratory animal models reflects human atherosclerosis remains unclear.[12]

Molecular and immunological studies: inflammatory mechanisms

The 'response-to-injury' hypothesis states that endothelial cell damage represents the crucial initial step in atherogenesis.[10] Indeed a variety of insults including all the conventional cardiovascular risk factors and infections are known to induce endothelial dysfunction and/or activation — thereby contributing to arterial structural damage and vasoconstriction, a prothrombogenic state, initimal proliferation, and enhanced expression of HLA antigens.[10,11,58,59] Endothelial cell activation may also lead to its expression of various inflammatory molecules.[10,11] These include:

1. adhesion molecules (E-selectin, P-selectin, vascular cell adhesion molecule-1 or VCAM-1, intercellular adhesion molecule-1 or ICAM-1) which promote leucocyte and platelet adherence and leucocyte penetration into the intima;[60]
2. cytokines (interleukin-1 or IL-1, IL-6, TNF-α) which may directly contribute to chronic endothelial cell damage, and stimulate hepatic synthesis of acute phase reactants such as C-reactive protein and fibrinogen;[61]
3. chemokines (e.g. monocyte chemoattractant protein-1 or MCP-1, IL8); and
4. growth factors (PDGF, bFGF).[10,11]

In vitro studies have demonstrated that macrophages, endothelial cells, and smooth muscle cells are capable of supporting the growth and proliferation of *C pneumo-*

niae.[62–65] It is possible that *C pneumoniae* may be carried by circulatory monocytes that originate from infected macrophages in the respiratory tract, and invade or contribute to endothelial dysfunction within the arterial wall.[35,66] At the distant endothelial surface, *C pneumoniae* may induce a chronic immune activation by cytokines such as IL-1, IL-6, and TNF-α,[61] and the expression of adhesion molecules.[67] In addition, *C pneumoniae* A-03 (a coronary strain) isolated has been shown to stimulate the production of monocyte chemotactic protein 1 (MCP-1), interleukin 8 (IL-8), and soluble intercellular adhesion molecule-1 (ICAM-1) in vitro.[68]

Monocytes and T-lymphocytes, attracted by various chemokines to the endothelial surface, themselves also produce a variety of cytokines (e.g. IL-1β, TNF-α), and these in turn recruit more leucocytes and increase the binding of LDL cholesterol to the endothelium.[10,69] Once adherent (anchored by adhesion molecules) to the dysfunctional endothelial cell, transendothelial penetration through the intact endothelial barrier into the subendothelial space occurs.[10] Many of these monocytes transform into macrophages loaded with oxidized LDL cholesterol, to become foam cells.[10] These activated macrophages and foam cells may release endotoxic oxidized LDL cholesterol, cytotoxic enzymes, growth regulatory factors, inflammatory cytokines, and procoagulants such as tissue factor.[10] A fibroproliferative response from the arterial smooth muscle cells is induced, leading to the formation of an early atherosclerotic plaque.[10,11,70]

Kalayoglu and Byrne in 1998 showed that *C pneumoniae* LPS could induce foam cell formation from human monocyte-derived macrophages.[71] Recently, *C pneumoniae* infection of human endothelial cells has been shown to stimulate the transendothelial migration of neutrophils and monocytes.[72] In addition, *C pneumoniae* has been shown to infect human umbilical vein cells with increased expression of tissue factor.[73] This could promote coagulation and platelet adhesion.[73] Systemically, *C pneumoniae* infection may induce the production of acute-phase proteins such as fibrinogen,[74,75] a known risk factor for cardiovascular disease; C-reactive protein,[76,77] a strong independent predictor of subsequent cardiovascular events; and neopterin,[78,79] a sensitive marker of macrophage activation.

Immunologically, the family of heat shock proteins (HSP) are highly conserved stress proteins with wide cross-reactivity.[5] They are induced in cells by adverse conditions such as heat and acute or chronic infection, and help the cells to deal with such conditions.[5] As the HSP are highly conserved, an autoimmune response with autoantibody formation is known to cross react between human HSP60 and chlamydial HSP60 in clinical inflammatory conditions such as pelvic inflammatory diseases caused by *Chlamydia trachomatis*.[80,81]

Interestingly, Kol and colleagues in 1998 discovered that chlamydial HSP60 and human HSP60 frequently localizes together within human carotid atherosclerotic plaques.[82] Both of these chlamydial and human HSP60 could activate macrophage TNF-α and matrix metalloproteinases—enzymes that can degrade connective tissue and cause plaque rupture.[82] *C pneumoniae* and chlamydial HSP60 were also reported to induce cellular oxidation of LDL cholesterol in atheroma.[83] Activation of macrophages may result in the increased production of IL12 and interferon-γ found in atherosclerotic lesions, and which maintain a process of chronic immune stimulation.[84–87] In particular, interferon-γ has been shown to

inhibit both the replicative life-cycle of *C pneumoniae* and recovery of viable *C pneumoniae* in tissue culture.[85–87] Hence HSP60 expressed by *C pneumoniae* even in its persistent, non-replicative state (PB), may promote atherogenesis by serving as antigens, and stimulate atherothrombosis by activating macrophages. In summary, autoimmune reactions to HSP could represent a link between infection-induced endothelial cytotoxicity and atherosclerosis.[5,88,89]

In contrast to the humoral immunity to *C pneumoniae* as discussed in the context of HSP, *C pneumoniae*-specific cell-mediated immunity in CAD has also been demonstrated.[90,91] A significantly increased cell-mediated activity, as measured by lymphocyte proliferative response to *C pneumoniae* antigens were observed in 93 patients with angiographic evidence of CAD, when compared to 115 control patients ($p < 0.001$).[91]

The process of atherogenesis and atherothrombosis may hence be attributed to infection through a number of local and systemic interactions (Fig. 7.3).[3,18,92] These inflammatory events include:

- direct infection of the arterial wall with smooth muscle proliferation
- endothelial dysfunction due to circulating endotoxin
- increased synthesis of inflammatory mediators such as C-reactive protein, leucocyte, cytokines and fibrinogen
- autoimmunity through cross-reactivity of heat-shock proteins with bacterial antigens
- lipoprotein disturbances
- monocyte activation
- enhanced activity of procoagulant mediators.

Specifically, *C pneumoniae* has been demonstrated to play an important role in most, if not all, of these inflammatory events.

Antibiotic intervention studies

Definitive proof that *C pneumoniae* causes atherosclerosis could come from antibiotic eradication of the agent, particularly in patients at risk of CAD.[5]

In 1997, two pilot intervention studies provided evidence that short courses of anti-chlamydial antibiotics (macrolides) may reduce secondary cardiovascular events.[93,94] In a UK-based study,[93] 220 consecutive male survivors of myocardial infarction were screened for anti-chlamydial antibodies. Increasing anti-chlamydial antibody titres were associated with increased cardiovascular events at 18 months follow-up. However, patients with elevated anti-chlamydial antibody (IgG seropositivity greater than 1:64) randomized to receive azithromycin (500 mg/day for 3 days, $n = 28$ or 500 mg/day for 6 days, $n = 12$) had a 5-fold reduction in cardiovascular events (odds ratio $= 0.2$; 95% CI 0.05–0.8; $p = 0.03$). The event rate in this group was similar to that in the seronegative group (odds ratio $= 0.9$; 95% CI 0.2–4.6, $p =$ NS). Conversely, patients with elevated anti-chlamydial antibody titre who were receiving placebo or not randomized to antibiotic or placebo, had a fourfold increased risk for experiencing adverse cardiovascular events compared with the seronegative group (odds ratio $= 4.2$, 95% CI 1.2-15.5; $p = 0.03$). Patients treated with azithromycin also had a fall in certain serum and monocyte activation markers of inflammation and procoagulation (monocyte integrins CD11b/CD11c, fibrinogen and leucocyte count; $p < 0.05$).[95]

In an Argentina-based study,[94] the

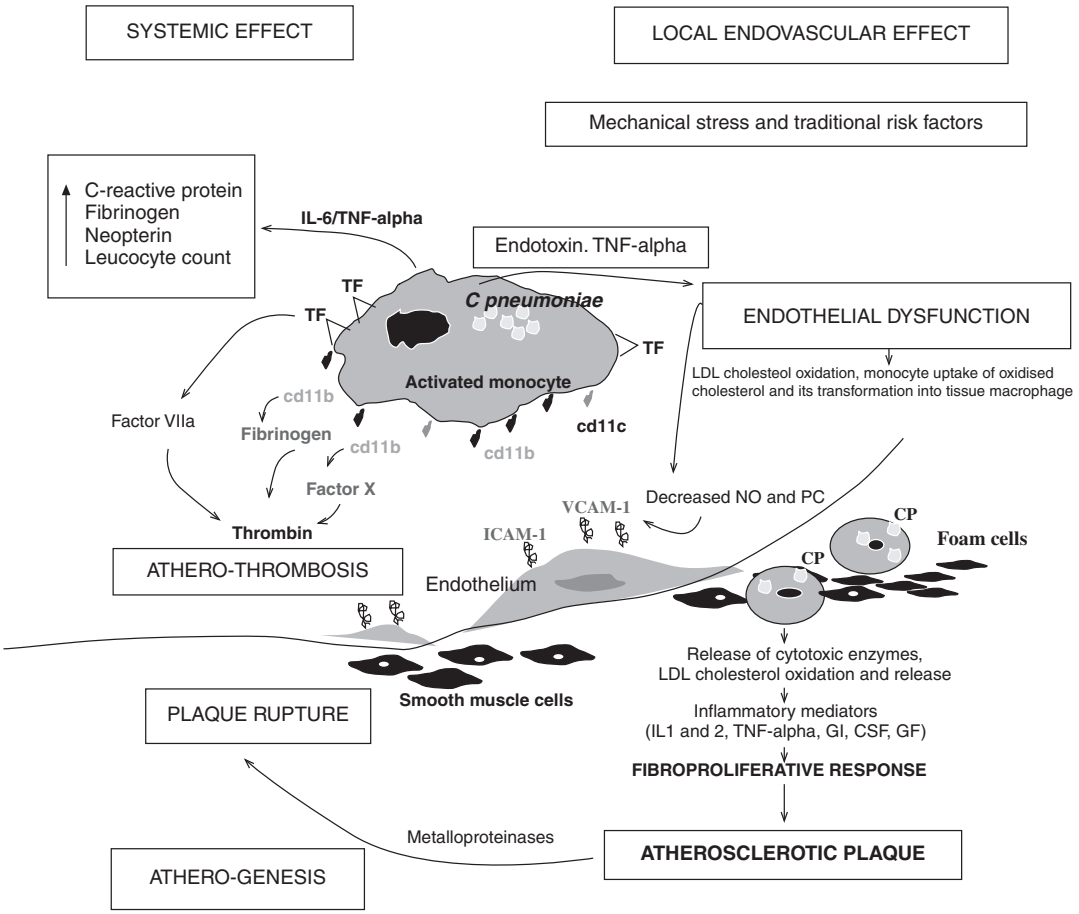

Figure 7.3
The roles of C pneumoniae*, monocytes, and inflammatory markers in atherothrombosis and atherogenesis: possible interplay between molecular biological and immunological mechanisms.*[92]
C pneumoniae *may cause respiratory tract infection and then be transported systemically to coronary artery by circulating monocytes. In conjunction with traditional atherosclerotic risk factors, infected monocyte may be activated and contributes towards endothelial dysfunction and subsequent foam cell transformation and inflammatory response in the subendothelial space. Monocyte activation and endothelial dysfunction also lead to secretion of cytokines and acute-phase proteins, expression of adhesion molecules, and up-regulation of tissue factor and monocyte integrins. These processes may either act independently or interact leading to atherothrombosis and atherogenesis.*
Cd11b/c = monocyte integrins, Cp = Chlamydia pneumoniae*, CSF = colony stimulating factor, GF = growth factor, GI = gamma interferon, ICAM/VCAM = Intercellular/Vascular cell adhesion molecules, IL = interleukin, LDL = low density lipoprotein, NO = nitric oxide, PC = prostacyclin, TF = tissue factor, TNF = tumour necrosis factor. (Adapted and modified from Gupta S, with permission).*[92]

Roxithromycin in Ischaemic Syndromes (ROXIS) study was another small study comparing the effects of oral roxithromycin 150 mg twice daily for 30 days with placebo, in patients with unstable angina or non-Q-wave myocardial infarction. At day 30, the combined adverse triple cardiac events rate of cardiovascular death, acute myocardial infarction and recurrent unstable angina, were 2% in the roxithromycin treated group versus 9% in the placebo group (unadjusted $p = 0.032$, adjusted $p = 0.06$). Yet, the adverse triple cardiac end-point rates in the placebo group versus roxithromycin group at day 90 and at day 180 revealed no significant difference.[96] Certain inflammatory markers such as C-reactive protein levels decreased more significantly in the roxithromycin group.[96]

In a later case-control study comparing 3315 patients with first-time myocardial infarction (MI) with 13 139 controls, MI patients were significantly less likely to have taken quinolones (adjusted odds ratio = 0.45, 95% CI 0.21–0.95) or tetracyclines (adjusted odds ratio = 0.70; 95% CI 0.55–0.90) in the preceding three years compared to controls, after adjusting for a number of confounders.[97] However, no such benefit was found for previous use of macrolides. This study provided indirect evidence for an association between micro-organisms susceptible to tetracycline or quinolone antibiotics and the risk of a first MI.

The recently reported Azithromycin in Coronary Artery Disease Elimination of Myocardial Infection with Chlamydia (ACADEMIC) study showed that 3-month treatment with azithromycin failed to prevent adverse clinical cardiovascular events at six months and at two years.[98,99] The antibiotic did appear to have some effects by reducing circulating inflammatory markers including C-reactive protein, interleukin-1, inetrleukin-6, and TNF-α levels, six months after active treatment.[98]

The macrolides used in these intervention studies could be acting through non-antimicrobial effects such as anti-inflammatory or plaque-stabilizing effects, thereby halting the progression of atherogenesis and atherothrombosis.[18,100,101] Other broad spectrum antibiotics with anti-chlamydial activity, such as tetracyclines, inhibit macrophage matrix metalloproteinases and may also potentially stabilize the atherosclerotic plaques.[102,103] Other plausible reasons for the apparent positive association between antibiotics and a reduction in CAD could be due to their activities against other infections linked to CAD, counteracting effects on other cardiovascular risk factors, unknown pharmacological effects unrelated to their antimicrobial properties, or simply due to chance in view of the small number of patients studied.

To establish the potential impact of antibiotics in the treatment and prevention of CAD requires adequately powered, randomized, double-blinded, placebo-controlled prospective studies. Several such trials are underway: these include:

- 'Weekly Intervention with Zithromax in Atherosclerotic-Related Disorders' (WIZARD)
- 'Might Azithromycin Reduce Bypass List Events' (MARBLE)
- 'Azithromycin and Coronary Events Study' (ACES)
- 'Pravastatin or Atorvastatin evaluation and infection therapy' (PROVE-IT).[18,104]

A total of nearly 20 000 patients with estab-

lished CAD will have been randomized, and results should be available in the next few years.

Is coronary artery disease an infection-mediated inflammatory disease?

Coronary artery disease is acknowledged as a multifactorial inflammatory disease. It is plausible that infection, by interacting with classical cardiovascular risk factors (such as hypertension,[105] smoking,[106] hyperlipidaemia,[107] age,[25,108] and male sex[108]), may predispose certain genetically-susceptible[109,110] people to atherosclerosis. Evidence already exists for such a 'modulator' role for *C pneumoniae*. Although each traditional cardiovascular risk factor may be synergistic with each other in the causation of CAD, it is unclear how exactly *C pneumoniae* may interact with these risk factors. Adequately powered studies will need to account not only for these potential confounding risk factors, but also to establish if even a relatively small, but clinically independent, causal role of *C pneumoniae* in CAD may exist.

The notion that microorganisms may cause inflammatory or immune-mediated, 'non-infectious' diseases is no surprise. *Helicobacter pylori* is now well-recognized clinically as an aetiological factor in the pathogenesis of peptic ulcer disease.[111] Epstein-Barr virus has been linked to nasopharyngeal carcinoma,[112] *Tropheryma whippleii* to Whipple's disease,[113] and mycobacteria have been identified in Crohn's disease[114] and sarcoidosis.[115]

Traditionalists will say that Koch's postulates need to be fulfilled before an infectious agent can be seen as a confirmed causal agent in atherosclerosis (Table 7.2).[5,116] The criteria include:

1. the microorganism should always be present in the diseased tissue;
2. viable microorganism could be cultured from the diseased tissue;
3. inoculation of microorganism into susceptible animal would produce disease;
4. microorganism could be detected in the pathological tissue from diseased animal.

Does the link between C pneumoniae *and CAD fulfil Koch's criteria (Table 7.3)?*

Chlamydia pneumoniae is, but not always, detected in atherosclerotic coronary arteries. Absence may be due to current inadequate laboratory detection techniques, scanty distribution of *C pneumoniae* in the diseased tissue, or even a 'hit and run' pattern of infection.[5] However, *C pneumoniae* has been found to localize preferentially in human atherosclerotic cardiovascular tissue,[37] although Koch's criterion 1 above was not always fulfilled. Live, viable *C pneumoniae* is cultured, but not always, from the atheroma.[45,46] This fulfils the stated Koch's criterion 2. In prospective human seroepidemiology observations, although the association between *C pneumoniae* and CAD may be weak and the underlying causative mechanism unclear, cumulative data do suggest prior *C pneumoniae* infection/inoculation is linked with subsequent development of CAD.[5,12] More directly, animal models have demonstrated that inoculation of *C pneumoniae* into susceptible animals such as rabbits or mice, can initiate atherogenesis.[5,12] Furthermore, *C pneumoniae* could be detected in the atherosclerotic tissue from the diseased human

Koch's criteria	Chlamydia pneumoniae *in coronary artery disease*	Helicobacter pylori *in peptic ulcer disease*
1. Microorganism always present in the diseased tissue	Not always	Not always
2. Viable microorganism could be cultured from the diseased tissue	Yes (not always)	Yes (not always)
3. Inoculation of microorganism into susceptible animal would produce disease	Yes	Yes
4. Microorganism could be detected in the pathological tissue from diseased animal	Yes	Yes

(Adapted from Ngeh J and Gupta S, with permission).[5]

Table 7.3
Koch's postulates for infectious diseases: Chlamydia pneumoniae *in coronary artery disease versus* Helicobacter pylori *in peptic ulcer disease.*

and animals.[5,12] Hence, Koch's criteria 3 and 4 were fulfilled, at least in animal model studies. It is noteworthy that not all the criteria are fulfilled for the well-recognized *Helicobacter pylori*–peptic ulcer link[5] (Table 7.3), and infectious diseases caused by fastidious microorganisms such as mycobacteria. Perhaps Koch's postulates need to be revised in chronic diseases?

Molecular biology and immunology studies had elucidated some important mechanisms, whereby infections such as *C pneumoniae* could participate and contribute directly to atherogenesis and atherothrombosis.[5,12] Antibiotic intervention studies in animals have shown indirect evidence on how *C pneumoniae*-induced atherosclerosis could be reversed by antibiotic treatment.[49,52] Results of antibiotic intervention trial studies in CAD in humans are awaited.

Conclusions

As the major clinical manifestation of atherosclerosis, coronary artery disease will remain the commonest cause of death worldwide. This is in spite of an increasing understanding of the pathophysiology, epidemiology, and advances of CAD treatment. The search and research of novel cardiovascular risk factors is hence justifiable.

The recognition of an inflammatory basis to the pathogenesis of atherosclerosis and CAD has provided a plausible link between

infection and CAD. Over the last decade, *C pneumoniae* has emerged as the strongest contender in the 'infectious' hypothesis of atherosclerosis. The majority of research evidence when viewed collectively, including seroepidemiological studies, pathological tissue examinations, animal model experiments, pathogenetic, molecular or immunological investigations, in addition to human antibiotic intervention studies, have implicated favourably a potential role for *C pneumoniae* in CAD.

The current research in the context of 'inflammation, infection, and antimicrobial therapy' in CAD will demand a collaborative approach. Undoubtedly, there is an impetus to develop novel anti-inflammatory/anti-chlamydial agents, and to study any additional anti-inflammatory properties of other therapeutic agents (such as the statins) currently used in the treatment of CAD. The positive results of the earlier pilot antibiotic intervention studies have stimulated a number of well-designed, adequately powered, placebo-controlled studies now in progress. If the outcome of these anti-chlamydial treatment studies confirm a reduction in adverse cardiovascular events, there will undoubtedly be an urgent need to develop a targeted approach of antibiotic treatment in the secondary prevention of CAD. The issues of primary prevention, antibiotic eradication regimens including the dosage and duration of therapy, non-antimicrobial properties and safety profiles of the antibiotics used will then all need further studies. The potential for widespread antibiotic misuse and resistance is another valid issue.

Although a coincidental link between *C pneumoniae* infection and CAD is still a possibility, evidence is increasingly against this. Nevertheless, definitive proof of a causal link is currently lacking. One cannot ignore the cluster of negative studies that have emerged. A future meta-analysis of all the large-scale antibiotic intervention trials (totalling around 20,000 patients with CAD) may help to clarify the nature of the link between *C pneumoniae* infection and CAD. Antibiotics, except in well-designed research settings, should not be used to treat CAD at present. We remain focussed on targeting and treating the established cardiovascular risk factors in CAD, and using therapeutic strategies of proven prognostic value such as aspirin, beta-blockade, angiotensin-converting enzyme inhibitors, and statin therapy for the secondary prevention of CAD.

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8

Unstable Coronary Syndromes: What is New?

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Introduction

The management of acute coronary syndromes without persistent ST segment elevation continues to be a challenge. As our understanding of the pathophysiology and natural history of this group of conditions changes, there is a corresponding expansion in our therapeutic targeting. Unstable angina and non-Q-wave myocardial infarction (NQWMI), which now account for the majority of admissions to coronary care units, are characterized by myocardial ischemia and share the same underlying pathophysiology of thrombus formation superimposed on a fissured or eroded atherosclerotic plaque. The high proportion of macrophages observed within ruptured plaques highlights an inflammatory process, which is also reflected in a number of markers such as C-reactive protein (CRP) measured systemically. Intraluminal thrombi, which limit blood flow but do not occlude the vessel, are common. The cardiac isoforms of troponin T and I are exclusively expressed in cardiac myocytes and when elevated reflect myocardial cellular necrosis. Current recommendations are that troponin T or I should be measured on admission in patients with suspected acute ischemic heart disease, and repeated 6 to 12 hours later.[1] Elevated levels of troponins and CRP are also strongly related to long-term risk of death from cardiac causes in patients with acute coronary syndromes.[2] The principal difference between unstable angina and NQWMI is the longer duration of arterial obstruction which results in myocardial necrosis in the latter group of patients.[3] There are prognostic differences also. In the TIMI IIIB trial,[4] NQWMI patients had a 70% greater risk of death or myocardial infarction (MI) at 6 weeks (8.6% NQWMI vs 5.0% unstable angina, $p = 0.05$). Table 8.1 outlines how also, despite antithrombotic therapy, patients with NQWMI have a significantly higher rate of reinfarction and death at 12 weeks.[5] While, long-term, 1-year unstable angina mortality can be as high as 12% (most of this occurring after the first months of hospital discharge),[6] it can be up to 15% in NQWMI.[7] Although the in-hospital mortality in NQWMI is lower, the long-term and cumulative prognosis in terms of morbid and fatal events is at least equal and possibly greater than in Q-wave MI. This reflects the higher recurrent angina and reinfarction rates attributable to residual jeopardized myocardium in NQWMI patients.[8] It has been estimated that if treatment guidelines[9] were adhered to then 1-year mortality could be reduced by a relative 22%.[6]

The aim of this chapter is to review the data supporting novel pharmacological and

	Recurrent angina (%)	Myocardial infarction (%)	Death (%)	Total (%)
Unstable angina	20	4	3	27
NQWMI	11	11	5	27

Data from Anderson et al 1995.[4]

Table 8.1
Primary endpoints at 12 weeks, unstable angina versus non-Q-wave myocardial infarction.

interventional therapies for patients with non-ST elevation acute coronary syndromes.

Antithrombotic therapy in unstable angina

Both aspirin and heparin have an established role in the management of acute coronary syndromes. Meta-analysis shows that there is a 33% reduction in risk of death or MI in unstable angina patients treated with aspirin and heparin compared to aspirin alone.[10] Because of the limitations of unfractionated heparin (UFH), which include short duration of action, poor bioavailability, unpredictable anticoagulant response and the risk of heparin-induced thrombocytopenia (HIT) and disease reactivation following early discontinuation, there is much current interest in the development of newer antithrombotic strategies. Low-molecular-weight heparins (LMWHs) offer potential benefits over standard heparin[11] and several clinical trials confirm this benefit.

Low-molecular-weight heparins

FRISC I and FRISC II

A number of studies have been conducted with LMWHs in unstable angina. The Fragmin during Instability in Coronary Artery Disease (FRISC) study[12] randomized 1506 patients with unstable angina and non-Q-wave MI to treatment with dalteparin sc or placebo twice daily for 6 days then once daily for the next 35–45 days. All patients also received aspirin. In the early phase there was a 63% relative risk reduction in the primary endpoint of death and MI. After 40 days, rates of death, new MI and occurrence of revascularization remained lower in the dalteparin group, but this benefit was confined to non-smokers. At the 4–5 month follow-up after treatment end, there were no significant differences in event rates between the two groups. These findings indicate that unstable lesions appear to remain active for weeks or months after the initial unstable episode, and that patients may benefit from more prolonged treatment.[13]

The FRISC II trial[14] investigated the long-term (three-month treatment phase) use of dalteparin or placebo in 2457 patients with unstable angina. The composite primary endpoint was death or MI. During the three-month double-blind treatment phase there was a non-significant decrease in the composite endpoint of 6.7% and 8.0% in the dalteparin and placebo groups respectively ($p = 0.17$). At 30 days this decrease was significant (3.1% vs

5.9%; $p = 0.002$). In the total randomized cohort, including the open label (in-hospital, 1–7 days) and double-blind treatment periods, there was a non-significant decrease in death and MI at three months, but there was also a significant 4.3% absolute and 13% relative decrease in the triple composite endpoint of death, MI and revascularization. However, these initial benefits were not sustained at six months. During the double-blind treatment phase there was an increased risk of major bleeding episodes with dalteparin (3.3% vs 1.5%), and minor bleeds were more common than with placebo (23% vs 8.4%). There was no difference in the rate of strokes between the two patient groups, and a higher rate of hemorrhagic stroke in the dalteparin group was outweighed by a higher rate of other strokes in the placebo group. Dalteparin is currently used for up to 8 days in unstable angina. Based on FRISC II, although no persistent benefit was shown, treatment with dalteparin for up to 30 days may be beneficial as a 'bridging therapy' until intervention is undertaken. FRISC II also compared an invasive strategy with a non-invasive strategy, which is discussed in more detail below.[15]

FRIC

The Fragmin in Unstable Coronary Artery Disease Study (FRIC)[16] of 1482 patients, compared dalteparin with UFH and placebo, in an acute and a prolonged phase of treatment. All patients in this study also received aspirin. During the first 6 days, with twice daily sc treatment, the rates of death, MI or recurrent angina was 7.6% in UFH-treated patients, and 9.3% in dalteparin-treated patients, with a borderline difference in deaths between the two groups, of 3 versus 11, respectively. During the double-blind once-daily treatment, prolonged phase of the study, the composite, primary endpoint of death/MI/recurrence of angina was 12.3% in both groups. The authors concluded that twice daily sc administration of dalteparin may be an alternative to UFH in the acute phase of unstable angina, whilst prolonged treatment at the lower dose does not confer additional benefit over aspirin alone.

ESSENCE

The Efficacy and Safety of Subcutaneous Enoxaparin in non-Q-wave Coronary Events (ESSENCE)[17] was a randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of enoxaparin in 3,171 patients who were also receiving aspirin. Patients received either enoxaparin sc 1 mg/kg twice daily or continuous UFH for 48-hours to 8 days. At 14 days the composite primary end-point of death, MI or recurrent angina was significantly lower, 16.6% in the enoxaparin group compared to UFH, 19.8%, $p = 0.019$, a relative risk reduction of 16.7%. At 30 days, the composite endpoint remained significantly lower with enoxaparin, 19.8% versus 23.3%. The rate of revascularization by 30 days was also significantly lower with enoxaparin, 27.0% versus UFH 32.2%, $p = 0.001$. The incidence of major bleeding at 30 days did not differ significantly between the two groups, 6.5% versus 7.0%, respectively. The authors concluded that the combination of LMWH and aspirin is more effective than UFH plus aspirin in reducing early ischemia-related clinical outcomes in patients with unstable angina or NQWMI. One year follow-up of ESSENCE shows persistent benefit with enoxaparin and a 10.4% overall risk reduction.[18]

TIMI IIA and TIMI IIB

The Thrombolysis in Myocardial Infarction (TIMI) IIA study[19] was a dose-ranging trial of enoxaparin in unstable angina, which showed that an acute phase regimen of enoxaparin 1.0 mg/kg every 12 hours, is associated with an acceptable rate of bleeding during the in-hospital phase. It also showed that there is a high rate of patient compliance during the home treatment phase, with prolonged fixed sc dosing with 60 or 40 mg twice daily for 14 days. TIMI IIB tested the benefits of uninterrupted treatment with enoxaparin during both the in-hospital and outpatient treatment phases (up to 35 days treatment). Results showed that the incidence of death, MI, and recurrent angina requiring revascularization at 8 days was significantly reduced in the enoxaparin group (12.4%) compared with the UFH group (14.5%) ($p = 0.048$).[20] This difference, which was achieved without an increase in major hemorrhages, was sustained for at least 43 days when the rates were 17.3% and 19.7% respectively.

A meta-analysis of the two trial results[21] shows that enoxaparin is associated with a 20% reduction in death and serious cardiac ischemic events that appeared within the first few days of treatment and the benefit was sustained for 43 days. This was not associated with an increase in major hemorrhage in the acute phase of treatment but there was an increase in the rate of minor hemorrhage. Enoxaparin is also being investigated in both arms of the Third Randomized Intervention Treatment of Angina Trial (RITA-3), a randomized trial of a conservative treatment strategy versus an interventional treatment strategy in patients with unstable angina.

A smaller study comprising 219 patients with unstable angina[22] treated with aspirin alone, aspirin and UFH or aspirin plus the LMWH, nadroparin, looking at major endpoints such as death/MI/recurrent angina/revascularization and major bleeds, also looked at the minor endpoints of silent ischemia and minor bleeding. Treatment with aspirin and nadroparin during the acute phase of unstable angina, was significantly better than treatment with aspirin alone or aspirin plus UFH.

Not all trials of LMWH have shown benefit in unstable angina/NQWMI. The FRAXIS trial[23] which compared the LMWH, fraxiparine and UFH (administered for 6 days), showed no reduction in events during the acute treatment phase. The reasons for this are not known, but some workers suggest that this trial supports the association that LMWHs are not all comparable.

A recent meta-analysis[24] of randomized trials of low-molecular-weight heparin and UFH shows that short-term treatment using either agent halves the risk of death in aspirin-treated patients with unstable angina. It also stated that there is no convincing difference in efficacy or safety between either type of heparin and that the evidence does not support the use of LMWH after 7 days. The meta-analysis has been criticized on a number of grounds,[25,26] including the fact that none of the 12 trials involved in the meta-analysis specifically compared durations of therapy, which might provide information about the most efficacious and cost-effective treatment. It is also criticized on the basis that it discounts the possibility of clinical differences between different agents and runs contrary to the findings from the meta-analysis of ESSENCE and TIMI IIB, showing conclusively that enoxaparin is superior to UFH. Clearly this debate is likely to proceed for some time.

Thrombin inhibitors

Thrombin promotes platelet aggregation and plays a key role in the pathogenesis of unstable angina and NQWMI. Heparin is not effective against clot-bound thrombin therefore direct thrombin inhibitors may offer additional therapeutic effects. Most clinical experience has been gained with hirudin. Hirudin is a potent specific thrombin inhibitor, which was initially isolated from the saliva of the medicinal leech (*Hirudo medicinalis)* and is now produced by recombinant technology.

GUSTO IIb

The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb compared a recombinant hirudin (desirudin) with UFH for 72 hours, in 12142 patients with acute coronary syndromes.[27] Patients were stratified according to the presence or absence of ST-segment elevation on the baseline ECG. There were 8011 unstable angina/NQWMI patients. At 24 hours the risk of death or MI was significantly lower in the group assigned to hirudin therapy compared to UFH (1.3% vs 2.1%; $p = 0.001$). The primary endpoint of death or non-fatal MI or reinfarction at 30 days was reached in 9.8% of the UFH group compared to 8.9% of the hirudin group ($p = 0.06$). The predominant effect of hirudin was MI or reinfarction and this was not influenced by ST-segment status. This effect was more pronounced early (at 24 hours) but dissipated over time. Hirudin treatment was associated with a higher incidence of moderate bleeding (8.8% vs 7.7%; $p = 0.03$).

OASIS

The Organisation to Assess Strategies for Ischemic Syndromes (OASIS) pilot study[28] compared the effects of low and medium doses of recombinant hirudin (lepirudin) with UFH in 909 patients with acute myocardial ischemia without ST elevation. Hirudin, especially at the medium dose, appeared to be superior to UFH in preventing ischemic outcomes. After stopping treatment however there was an increase in events in the low dose group at 24 hours and at 5 days in the medium dose group.

The OASIS-2 trial[29] randomised 10141 patients to medium dose hirudin or UFH for 3 days. The primary end-point of cardiovascular death and MI at 7 days was reached in 3.6% of the hirudin group vs 4.2% in the UFH group ($p = 0.069$). The combined rate of cardiovascular death and MI was reduced by 24% (2.0% vs 2.6%; $p = 0.036$) and the rate of cardiovascular death, MI and recurrent angina was also reduced by 22% (3.2% vs 4.0%; $p = 0.018$). Benefits were maintained throughout the 35-day follow-up. On stopping treatment, events occurred in both groups at the same rate, reflecting the continued presence of coronary thrombus. But there was no evidence of clinical rebound following drug withdrawal. Hirudin was associated with a reduced need for revascularization. There was a statistically significant increase in bleeds in the hirudin treated patients, due primarily to an increase in minor and moderate hemorrhages; only 0.2% of patients required blood transfusions. There was only one hemorrhagic stroke in the study. Combining the results of the two OASIS trials there is a significant 19% reduction in death/MI at 7 days ($p = 0.034$).

Hirudin was also studied in the TIMI 9B trial[30] which showed no benefit with the drug in acute MI. However when this is combined with the data from the two OASIS trials and

	Cardiovascular death/MI at 3 days			
	Heparin (%)	*Hirudin (%)*	*Risk ratio (%)*	p *value*
OASIS-1	2.7	1.7	0.62	0.29
OASIS-2	2.6	2.0	0.76	0.035
GUSTO IIb	4.6	3.4	0.73	0.0004
TIMI 9B	3.1	3.8	1.22	0.301
Total	4.2	3.2	0.78	0.0004

Table 8.2
Hirudin compared in trials with unstable angina.

GUSTO IIb, hirudin is associated with a 22% reduction in cardiovascular death/MI at 3 days[31] (Table 8.2).

In summary, hirudin appears to be superior to UFH in unstable angina/NQWMI, with all the benefit occurring during the treatment period. Reactivation of coagulation has been shown[32] after stopping infusion of hirudin (and unfractionated heparin), which suggests that a longer course of antithrombotic therapy may be necessary for thrombus passivation. While it is unlikely that hirudin will be promoted commercially for unstable coronary syndromes, other thrombin inhibitors are now under investigation.

Warfarin

The effects of long-term warfarin at two intensities has been studied in patients with unstable angina/NQWMI in two consecutive randomized controlled trials.[33] Long-term treatment with moderate-intensity warfarin (INR, 2.0–2.5) plus aspirin, but not low-intensity warfarin (INR 1.5) plus aspirin, appears to reduce the rate of recurrent ischemic events. These promising results have laid the ground for a larger study of 4000 patients who will be randomized to moderate-intensity warfarin (INR 2–3) and aspirin versus aspirin alone after receiving iv antithrombin therapy.

Nicorandil

It is important to aggressively reduce myocardial ischemia in patients with unstable angina. A double-blind, prospective, randomized trial[34] of 243 patients indicated that the addition of the potassium channel opener, nicorandil, significantly reduces the frequency of ischemic episodes and tachyarrhythmias. The majority of these unstable angina patients were treated with aspirin, beta-blocker and a calcium antagonist, and over 60% received UFH. Although primarily a safety study, this did show that further benefit may accrue with vigorous pharmacological treatment.

Lipid-lowering therapy

The widespread use of lipid-lowering therapy with HMG Co-reductase inhibitors (statins) is now firmly established for secondary preven-

tion in coronary heart disease. In the 4S study, 4444 patients with angina or previous MI and cholesterol 5.5–8.0 received simvastatin 20–40 mg or placebo. There was a significant improvement in survival over 5.4 year follow-up in the treatment group.[35]

CARE then looked specifically at lower cholesterol levels in the post-acute myocardial infarction (AMI) population. There was a 24% reduction in risk of fatal coronary events and non-fatal AMI in the treatment group (pravastatin 40 mg). Furthermore, there was a reduction in the need for coronary revascularization procedures and the stroke risk was reduced (26% and 31% respectively).[36]

HMG Co-A reductase is the rate-limiting enzyme in cholesterol biosynthesis. Inhibition reduces intracellular cholesterol in the liver, which in turn stimulates a compensatory increase in hepatic LDL receptors. This promotes clearance of LDL-cholesterol from the plasma. Non-lipid effects of statins have also been described, such as reduction in plasminogen activator inhibitor 1 (PAI-1), coronary plaque stabilization, effects on endothelial function, and anti-inflammatory effects, which have been of particular interest in unstable coronary syndromes. In a subgroup of the CARE study, evidence of inflammation as measured by serum CRP and serum amyloid A (SAA) was associated with an increased risk of recurrent coronary events. Therapy with pravastatin reduced this risk supporting a non-lipid effect of this agent. [37]

LIPID is the largest multi-center statin trial so far (9014 patients), again using pravastatin 40 mg.[38] It broadened its entry criteria to older patients, and included more diabetics and more women than previous trials. Importantly it also included patients with unstable angina as well as acute MI. Again coronary and overall mortality were reduced.

These unequivocal findings led to the MIRACL study (Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering).[39] It investigated whether early, rapid, and profound cholesterol lowering therapy with atorvastatin could reduce early recurrent ischemic events in patients with unstable angina or non-Q-wave acute MI. 3000 patients were randomized to either 80 mg atorvastatin or placebo for a period of 3 months.

The primary endpoint was a composite of death, MI, and refractory recurrent ischemia requiring hospitalization. The initial results were presented at the American Heart Association 2000. 14.8% of patients on atorvastatin demonstrated a primary endpoint versus 17.4% on placebo (16% reduction, $p = 0.048$). This 16% reduction was primarily due to a favorable effect of atorvastatin on recurrent symptomatic myocardial ischemia (26% reduction, $p = 0.02$). Levels of LDL fell by 40% in those patients treated with atorvastatin.

This trial suggests statin therapy should be initiated immediately in unstable coronary syndromes.

The 'superaspirins'

Aspirin is a comparatively weak antiplatelet agent, which acts on only one of the many pathways to platelet activation. Thus, there has been a search for alternatives, notably the thienopyridines, ticlopidine and clopidogrel, which inhibit platelet aggregation induced by adenosine diphospate (ADP). Initially the CAPRIE trial compared long-term treatment with clopidogrel versus aspirin in patients with recent ischemic stroke, MI or peripheral vascular disease.[40] It showed a modest benefit with clopidogrel (8.7% relative risk reduction

in events). The Clopidogrel in Unstable Angina to Prevent Recurrent Ischaemic Events (CURE) trial recently reported on whether treatment with the *combination* of clopidogrel and aspirin is superior to aspirin alone when initiated early and continued long term in the prevention of major cardiovascular events, specifically in patients with acute coronary syndromes.[41] The trial randomized 12 564 ACS patients aged ⩾60 years to aspirin alone (75–325 mg per day) or aspirin plus clopidogrel. Clopidogrel was given as a 300-mg loading dose followed by a regular chronic dose of 75 mg per day. Patients were followed for 3–12 months (average 9 months). The primary endpoint of cardiovascular death, MI and stroke were significantly reduced in the treatment group (11.4% vs 9.3%, $p < 0.0001$). There were significantly more patients with major bleeding in the clopidogrel group than in the placebo group (3.7% vs 2.7%, $p = 0.001$) but there were not significantly more patients with episodes of life-threatening bleeding (2.1% vs 1.8%, $p = 0.13$) or hemorrhagic strokes.

GP IIb/IIIa receptor antagonists

Use during intervention

The platelet glycoprotein IIb/IIIa receptor antagonist class of agents has been developed following the understanding of the pivotal role of platelets in the pathogenesis of coronary thrombosis and the benefits of antiplatelet therapy.[42,43] When activated, the receptor develops a high affinity for fibrinogen and the propagation of platelet aggregation by cross-linking with this ligand results in thrombus generation.[44] IIb/IIIa antagonism is mechanistically attractive as an antiplatelet strategy because, in contrast to aspirin and the ADP inhibitors which reduce platelet activation, it blocks the 'final common pathway' of platelet aggregation. The remarkable efficacy of abciximab, the first IIb/IIIa blocker, was demonstrated in reducing the complications of high risk angioplasty in the landmark use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty (EPIC) study (Table 8.3),[45] and subsequently in lower risk angioplasty, and stenting in the Evaluation of Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome of c7E3 IIb/IIIa Receptor Blockade (EPILOG) study

Endpoint	*30 days*	*6 months*	*3 yrs*
Placebo (%)	12.8	35.1	47.2
ReoPro (%)	8.3	27	41.1
p value	0.008	0.001	0.009

Data from OASIS 1997.[28]

Table 8.3
Results of the EPIC study.

and the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) study (Tables 8.4 and 8.5).[46,47] Following this, a number of unstable angina studies have been reported.

In the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial, abciximab was compared to placebo given during the 18–24 hours before planned percutaneous transluminal ballon angioplasty (PTCA) for refractory unstable angina and continued for an hour after the procedure. All patients had coronary angiography and a culprit lesion amenable to treatment with PTCA identified prior to randomization. 1266 patients were studied and the combined primary endpoint of death, MI or urgent revascularization was significantly reduced by 28.9% (15.9%–11.3%, $p = 0.012$) compared with placebo at 30 days. It is important to note that the benefit of abciximab was predominantly seen in those patients with a Troponin T elevated above 0.1 ng/ml. This emphasizes the importance of risk stratification. This benefit was not however sustained at 6 months.[48] It has been suggested that the lack of sustained benefit was due to the absence of a 12-hour post procedure infusion as used in EPIC. This is possible, but as the study stands, no sustained benefit was shown, in spite of early efficacy. Interestingly in this

Endpoint	*30 days*	*6 months*
Placebo (%)	11.7	25.8
ReoPro + standard heparin (%)	5.4	22.3
p value (vs placebo)	<0.001	0.04
ReoPro + wt-adjusted heparin (%)	5.2	22.8
p value (vs placebo)	<0.001	0.07

Data from OASIS-2 1999.[29]

Table 8.4
Results of the EPILOG study.

Endpoint	*30 day (%)*	p *value (vs placebo)*
Stent + placebo	10.8	
Stent + ReoPro	5.3	<0.001
POBA + ReoPro	6.9	0.007

Data from Antman 1996.[30]

Table 8.5
Results from the EPISTENT study (n=2399).

study population, in the interval between the initiation of abciximab therapy and the planned PTCA, there was a significant reduction in MI with abciximab when compared with placebo. This was a pre-angioplasty treatment study and it may not be possible to generalize the findings to the medical management of unstable angina. Nevertheless, the results suggested that this class of drugs might be beneficial in unstable angina and a number of studies have followed.

Use for medical management of unstable angina

Studies of the medical therapy of unstable angina are complicated by the fact that a number of patients are likely to go on to angiography and angioplasty with varying rates in different trials. The four major early studies of IIb/IIIa antagonism as *medical* therapy in unstable angina have been dubbed the '4Ps': Platelet Receptor Inhibition for Ischemic Syndrome Management (PRISM), Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM PLUS), international randomized controlled trial of lamifiban heparin or both in unstable angina (PARAGON) and Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrelin Therapy (PURSUIT), (Table 8.6). The patients in these studies received aspirin in addition to the heparin and IIb/IIIa blocker protocols.

PRISM

PRISM randomly allocated 3232 patients with unstable angina or NQWMI to a 48-hour tirofiban infusion or heparin. Angiography and revascularization in the first 48 hours was discouraged. The primary composite endpoint of death, MI or refractory ischemia was significantly reduced by 33% (5.6%–3.8%, $p = 0.01$) during the first 48 hours in the tirofiban group but this was not sustained at 7 or 30 days.[49] Further analysis revealed that there was a significant 36% decrease in death at 30 days in the tirofiban group. In the medically treated subset of 1999 patients, death/MI was decreased by a significant 42% at 30 days. There was no difference in major bleeding between the groups.

PRISM PLUS

PRISM PLUS studied a higher risk group than PRISM with a 90% baseline rate of ECG ST and T wave changes compared with 39% in PRISM. 1915 patients with unstable angina or NQMI were randomly allocated to receive tirofiban, heparin, or heparin and tirofiban. The tirofiban infusion was for a minimum of 48 hours. Patients in the tirofiban-only group suffered excess mortality and this arm was therefore prematurely terminated. In the remaining two arms, a significant improvement in the primary composite endpoint of death, MI or refractory ischemia of 32% (17.9%–12.9%, $p = 0.004$) at 7 days was seen. This was sustained at 22% (22.3%–18.5%, $p = 0.03$) at 30 days, persisting, albeit diminished to 19% (32.1%–27.7%, $p = 0.02$) at 6 months.[50] However, 90% of the patients in this trial underwent coronary angiography during the study period. 30.5% underwent PTCA during their hospital stay. Furthermore, the benefit was greatest in those patients undergoing revascularization, and specifically angioplasty (Table 8.7). It is therefore difficult to use these data to advocate use of IIb/IIIa receptor antagonists in a purely 'medical' setting. Interestingly, a significant reduction in ischemic events *prior to* percuta-

Study	Drug	30-day composite endpoint		
		Drug	Placebo	p value
PRISM	Tirofiban	15.9	17.1	0.34
PRISM PLUS	Tirofiban	18.5	22.3	0.03
PARAGON	Lamifiban	11.3*	11.7	0.80
PURSUIT	Eptifibatide	14.2	15.7	0.04

* high- and low-dose lamifiban

Table 8.6
30-day results from the '4P' studies.

neous coronary intervention (*PCI*) was seen, as was the case in the CAPTURE and PRISM studies.

PARAGON

In the PARAGON study, 2282 patients with unstable angina or NQWMI were randomly allocated in a factorial design to receive low dose lamifiban with or without heparin, high-dose lamifiban with or without heparin or placebo with heparin. Lamifiban was infused for 72–120 hours. Angiography in the first 48 hours was discouraged. There was no significant difference in the composite endpoint of death or non-fatal MI between the placebo and treatment groups at 30 days. At six months the composite was significantly reduced by 23% (17.9%–13.7%, $p = 0.027$) in the low dose lamifiban group compared with control, and the high dose lamifiban group gave an intermediate non-significant outcome. The addition of heparin to the lamifiban groups caused increased bleeding in the high dose group with a similar rate of ischemic

	Tirofiban/ heparin (%) (n = 773)	Heparin alone (%) (n = 797)	Relative risk	Confidence intervals
PTCA	18.1	24.7	0.67	0.46–0.98
CABG	28.7	32.3	0.80	0.55–1.16
Medical	14.8	16.8	0.87	0.60–1.25

Table 8.7
PRISM PLUS. Recurrent ischemia/death/MI at 30 days.

outcomes. In the low dose group however bleeding was not increased but the ischemic event rate was significantly decreased compared with control by 30% (17.9%–12.6%, $p = 0.025$) at 6 months.[51] It is difficult to explain why the low-dose lamifiban was more effective than the higher dose, and although lamifiban appears to be active and may be useful clinically, this must raise queries about the conclusions. Bleeding was more common in the high dose but not the low dose treatment group.

PURSUIT

PURSUIT was a large study recruiting 10948 patients with unstable angina or NQWMI. Patients were randomly assigned to receive a bolus plus infusion of eptifibatide or placebo. The study drug was infused until hospital discharge or 72 hours. Heparin use was encouraged but not required or randomized. The 30-day composite endpoint of death or nonfatal MI was reduced by a very modest 9% (15.7%–14.2%, $p = 0.04$), which was of borderline significance.[52] Bleeding was more common in the treatment group, but there was no increase in hemorrhagic stroke.

GUSTO IV-ACS

The Global Utilization of Strategies to Open Arteries IV-Acute Coronary Syndromes (GUSTO IV-ACS) was a large-scale trial of adjunctive abciximab in patients in whom an interventional strategy was not initially planned. 7800 patients with unstable angina were treated with aspirin, heparin and other standard medical therapy. Patients were only required to have 5 minutes of anginal pain at rest, and either have a positive troponin or at least 0.5 mm ST-segment depression at rest. They were randomized to receive either a 24-hour infusion of abciximab, a 48-hour infusion of abciximab or placebo. The study primary endpoint was death or MI at 30 days. There was no significant incremental benefit of adjunctive abciximab therapy in the study population. In fact, there was a trend towards worse outcome in both 30-day combined endpoint and mortality in the 48-hour abciximab infusion group. For the troponin positive patients, death/MI at 30 days was 9.7% for placebo, 10.2% for 24 hour abciximab and 11.7% for 48 hour abciximab. Although delegates were surprised when the findings of GUSTO IV-ACS were presented at the European Society of Cardiology,[53] a number of potential reasons for the negative findings have been put forward. The most compelling of these is that the study group was not a very high risk cohort: indeed in the placebo group the 30-day MI rate was only 8% (compared with the 11% predicted). There has also been concern that the trial was underpowered. Importantly, fewer than 5% of patients underwent revascularization, which is far fewer than might be expected even with a conservative strategy. These provisional results await confirmation.

Oral IIb/IIIa antagonists

There are a number of drugs in development and undergoing phase III trials, including the oral agents which give the potential for a longer duration of therapy. This is particularly attractive since following coronary plaque rupture and thrombosis the damaged endothelium takes time to heal, further plaque events may occur, and the hemostatic system remains activated for several months.[54] Continued platelet inhibition during this time is logical and may be beneficial. Disappointingly however, Searle announced in January 1999

the withdrawal of their major oral fiban development program. This was on the basis of the results from two large phase III trials of Xemilofiban and Orbofiban in PTCA and acute coronary syndromes respectively, which failed to show significant clinical benefit. The most recent trial was BRAVO – Blockade of the IIb/IIIa Receptor to avoid Vascular Occlusion. This trial enrolled 9200 patients. The data and safety monitoring committee met in December 2000 to review the latest results and found that lotrafiban was associated with an increased mortality versus placebo (2.7% vs 2.0%, $p = 0.022$). [55] Furthermore, the drug was associated with an increased incidence of serious thrombocytopenia (2.2% vs 0.5%) and was also associated with more major bleeding (4.2% vs 1.3% respectively) ($p < 0.0001$). It has been argued that the failure of the oral agents was due to inadequate receptor occupancy and indeed a partial agonist effect when compared with those administered intravenously. Interestingly, however, the excess mortality seen in BRAVO appeared to be related to sudden death rather than thrombotic episodes (non-fatal MI and stroke).

The present

In addition to aspirin and an antithrombin there is therefore a debate regarding whether, and in what circumstances, augmented antiplatelet treatment with a IIb/IIIa inhibitor should be used to treat unstable angina in practice. In addition to the debate about efficacy, these agents are expensive and may result in hemorrhagic complications. At present the evidence favours limiting the use of IIb/IIIa antagonists in the setting of unstable angina in high risk cases due to undergo percutaneous intervention. It is also possible that the highest risk medically managed patients may benefit. However, such very high risk patients, outside the setting of a clinical trial, will often undergo invasive management and therefore be likely to benefit from IIb/IIIa blockade anyway. Further studies are needed to evaluate the optimal timing of initiation, and the duration of treatment.

The future

The situation seems fairly clear regarding IIb/IIIa inhibition in high-risk unstable angina with planned PCI. In lower-risk groups the trials are disappointing so far, but it is possible that with different agents and dosing schedules a benefit may be shown and the results of further trials are awaited.

Intervention in unstable angina

There are two new areas of interest in the interventional management of patients with acute coronary syndromes. The first is an increase in the understanding of risk stratification, specifically the identification of which patients should be referred for invasive and then interventional therapy. The second area concerns the advance in adjunctive pharmacological therapies available that reduce the complication rates and long-term outcome in patients undergoing these high-risk procedures.

Risk stratification: who should be referred for angiography and intervention?

Coronary artery intervention by means of PTCA, with or without stent deployment, offers a powerful tool in the management of *some* patients with acute coronary syndromes. Of all the patients admitted with unstable angina or NQWMI, approximately 90% can be symptomatically stabilized by the application of aggressive medical therapy,[56–58] the spectrum and potency of which, as has been discussed above, are increasing all the time. This leaves approximately 10% of this patient group who do not settle on maximum medical therapy. Such patients cannot be sent home and at present consume vast (yet unmeasured!) financial resources by their bed occupation. It has recently become apparent, however, that a significant subgroup of the patients whose symptoms do settle, are still at high risk of cardiac events, and benefit from revascularization.

It is imperative to be clear that, for two main reasons, referral for invasive assessment with a view to either percutaneous or surgical intervention is not appropriate for the whole group. Firstly, for purely logistic reasons, the facilities are not available to achieve this goal and they never will be. Secondly, there is clear evidence from both the TIMI-IIIb[59] and VANQWISH[60] studies that a policy of global invasive assessment and treatment of all these patients, regardless of symptoms or evidence of ischemia, is not beneficial overall and is probably harmful to some patients. Thus, in TIMI-IIIb 1473 patients with unstable angina or NQWMI were randomized to conservative or invasive strategies, regardless of symptoms or signs of on-going ischemia. The combined endpoint of death, further MI or progression to heart failure was seen in 18.1% of the conservative group and 16.2% of the invasive group (p = NS). Similarly, in the VANQWISH study 920 patients with NQWMI were randomized to conservative or invasive strategies. The in-hospital mortality was actually higher in the invasive group in this study although preliminary results from long-term follow-up indicate little difference between the groups. It is interesting to note that the crossover rates from the conservative to the invasive arms in these studies are very high (64% in TIMI-IIIb). Such high rates of crossover make meaningful analysis of outcome problematic, but illustrate effectively the fact that a proportion of such patients are likely to end up on the catheter laboratory table regardless of the degree of invasive 'aggression' of the attending physician! It also considerably weakens the cost efficiency arguments of the health economists. Having accepted that not all of this group should be referred for invasive assessment it then becomes essential to clearly define which groups *should* be referred. Patients with continuing symptoms and/or evidence of ongoing ischemia select themselves: they are both at high risk of further cardiac events and also sitting in a hospital bed unable to go home. These patients should all undergo angiography with a view to revascularization (Figs 8.1 and 8.2).

Recent evidence has unearthed another method of identifying patients in this population who are at high risk of further cardiac events. It has become apparent that the underlying pathophysiological mechanism producing the syndrome of unstable angina involves a localized inflammatory reaction based around and upon an eroded or fissured plaque. This reaction involves platelet activa-

tion and aggregation with thrombus formation inevitably leading to transient reductions in blood flow (Fig. 8.3). This dynamic process can be detected biochemically by elevations in the serum concentrations of C-reactive protein (CRP) and can result in variable degrees of myocardial damage. The mildest forms of damage can be detected by release of the cardiac-specific proteins, troponins T and I. Recent data have demonstrated that the admission level of [CRP] correlates with outcome in patients with unstable angina.[61,62] Furthermore, elevated admission levels of 'troponin T and I' also carry prognostic value.[63–66]

Having decided that those with raised biochemical markers of ischemia are at most risk, it does not necessarily follow that early revascularization improves outcome in these patients. There is now, however, very strong evidence for exactly this approach.

FRISC II (mentioned above in the context of low-molecular-weight heparins) randomized 2457 patients with chest pain and non-ST elevation ECG changes or raised biochemical markers (troponin T, CKMB) to an early invasive or conservative treatment strategy.[67] Fifty-eight percent of each group were troponin

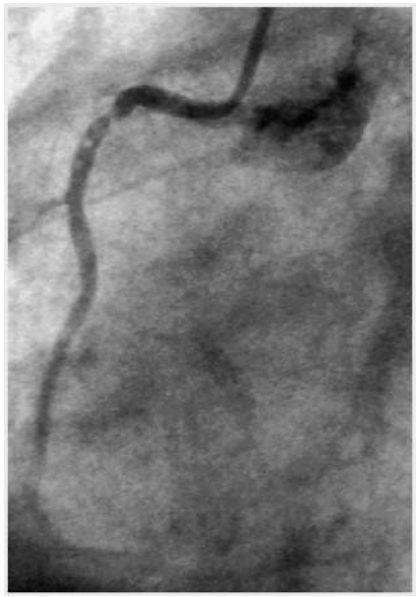

Figure 8.1
Right coronary angiogram of a patient presenting acutely with chest pain and inferolateral ST depression showing a discrete thrombus in the mid vessel.

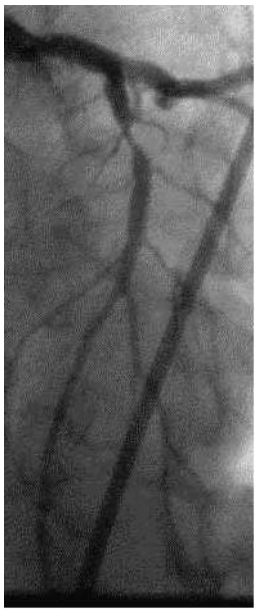

Figure 8.2
Left coronary angiogram in left anterior oblique projection with cranial tilt showing a tight stenosis in the left anterior descending coronary artery. The patient was a 45-year-old male who presented with chest pain and anterior T wave inversion.

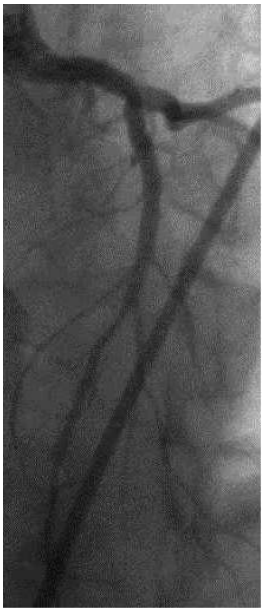

Figure 8.3
Left coronary angiogram in left anterior oblique projection with cranial tilt in same patient as in Fig. 8.2. The lesion has now been treated by the deployment of a 3 × 12mm stent. The patient was treated with abciximab bolus and infusion and went home two days later.

positive (troponin T > 0.1 ng/ml). Invasive patients were investigated with coronary angiography and revacularized within 10 days. Suitable patients with one- or two-vessel disease underwent PCI, and those with three-vessel or left main disease went for bypass surgery. Non-invasive patients with refractory angina despite maximal medical therapy, or with a strongly positive pre-discharge exercise test, also underwent angiography. Even so, only 10% of the non-invasive arm crossed over to the early invasive strategy, distinguishing this trial from previous studies (TIMI IIIb and VANQWISH above). Seventy-one percent of the invasive group were revascularized within 10 days versus 9% of the non-invasive group, compared with 78% and 43% at one year.

Angina symptoms and re-admission were halved by the invasive strategy. At six months there were significant reductions in the composite endpoint of death and MI (9.4% vs 12.1%, $p = 0.03$). At one year benefits were increased in the invasive group where mortality was 2.2% versus 3.9% in the non-invasively treated group ($p = 0.016$), and rates of MI were 8.6% versus 11.6% respectively ($p = 0.015$). The composite of death/MI was 10.4% versus 14.1% ($p = 0.005$). The results show that after one year in 100 patients, an invasive strategy saves 1.7 lives, prevents two non-fatal MIs, and 20 re-admissions, and provides earlier and better symptom relief at the cost of 15 more patients with coronary artery bypass grafting (CABG) and 21 with PTCA. The authors conclude therefore that an invasive approach should be the preferred strategy in patients with unstable coronary syndromes and signs of myocardial ischemia or raised levels of biochemical markers of necrosis.

This was the first randomized controlled trial to show a benefit for the early invasive approach. Interestingly in those undergoing PTCA, use of abciximab was extremely low (10%), and stents were used in only 61% of the invasive group.

The TACTICS-TIMI 18 study was presented at the American Heart Association 2000 scientific sessions in New Orleans, and is another study comparing early invasive and conservative strategies, this time incorporating GP IIb/IIIa inhibition with tirofiban in both arms.[68] 2220 patients with unstable angina or non-ST elevation MI were treated with

medical therapy and tirofiban (Aggrastat) infusion for 48–108 hours. They were randomized to invasive investigation at 4–48 hours. The primary endpoint was the combined endpoint of death, MI, or re-hospitalization for acute coronary syndromes at six months. The primary endpoint was reached in 19.4% of the conservative group versus 15.9% of the invasive group ($p = 0.025$). Importantly, there was an absolute reduction of 10% (24% down to 14%) in those with a positive troponin. These preliminary data further support the early invasive strategy and again show the benefits of GP IIb/IIIa therapy are maximal in those undergoing revascularization. Furthermore, the benefits are confined to the troponin positive group, and those with ECG changes. This trial has not as yet shown a mortality benefit however. Further results are awaited.

The current recommendation, therefore, is that only the patients at highest risk of further cardiac events should be referred *in the early phase* for invasive assessment with a view to revascularization. Such patients are not only those with refractory symptoms and/or ischemia but include those whose symptoms settle but have 'elevated' admission levels of troponin (troponin T > 0.1 ng/ml).

Improving early and late outcome following PTCA in acute coronary syndromes

Some evidence suggests that overall procedural success of PTCA may be lower in patients with acute coronary syndromes than in stable patients,[69–72] although such data were derived at a time of inferior equipment and lower stent rates. Out of a total of 560 cases, procedural success rates at the London Chest Hospital over the year 1998 were 87% for stable patients and 89% for those with unstable angina.[73] The stent rate in both groups was over 90%. However, there have been clear historical data to support the concept that the overall incidence of complications associated with PTCA is higher in patients presenting with unstable symptoms. Factors such as unstable, inflamed coronary plaques with overlying thrombus and the presence of various forms of anticoagulant and antiplatelet agents perhaps make this inevitable.

Two main categories of complication can be seen in PTCA, namely the short and the longer term. The most important short-term complications are associated with acute closure of the coronary artery, which may occur as a result of either vessel dissection or thrombosis within the first 24 hours. Patients with acute coronary syndromes are at elevated risk of such complications. Acute vessel closure is associated with myocardial damage, death and the need for urgent revascularization.[69] Less dramatic acute loss of flow in side branches of the coronary artery being intervened upon can also occur during or soon after the procedure. These events are also sometimes associated with myocardial damage with elevated levels of creatine kinase and there is increasing evidence that this does not represent a completely benign outcome.[74] Stent deployment is a highly effective way of treating coronary dissection and reducing the complications that are derived from it. Stents are themselves associated with the development of thrombosis, although fortunately this complication is reduced in frequency in both stable and unstable patients by the antiplatelet regimen of aspirin and ticlopidine,[75] and more recently aspirin and clopidogrel, a structurally

similar agent with less side effects.[76,77] The longer-term complications of PTCA are dominated by the development of restenosis. Stent deployment has again been shown to significantly reduce the incidence of restenosis,[78,79] mainly by increasing the acute gain achieved in vessel diameter during the procedure. Optimally deployed stents can, according to recent data, reduce the incidence of restenosis to 10–15% at 6 months[80] compared to rates of 30–50% in patients treated with balloon angioplasty alone.

The higher risk of acute ischemic (main vessel closure, side branch loss) complications in unstable patients, but also perhaps longer-term requirement for revascularization, has stimulated considerable research. The most important product of this research activity so far is the antiplatelet agent, abciximab (ReoPro, Centocor BV). Abciximab is the Fab fragment of a human-murine chimeric antibody that occupies the platelet IIb/IIIa receptor, thereby inhibiting aggregation, as described above. Such a mechanism of action can be employed as a potent defensive tool against the thrombus-mediated acute ischemic complications that occur with particular frequency in 'high risk' coronary intervention. As previously mentioned, there are now three studies that have specifically addressed the benefits of abciximab under these circumstances.

The EPIC study[45] recruited 2099 patients undergoing high risk PTCA/atherectomy who were randomized to receive ReoPro bolus (0.25 mg/kg) plus infusion (10 mg/min for 12 hours) or placebo bolus and infusion, in addition to routine aspirin and heparin therapy. The composite endpoint consisted of death plus non-fatal MI plus requirement for urgent revascularization. There was a significant reduction in the composite endpoint at 30 days, 6 months and 3 years (Table 8.3) in the abciximab group. It is notable, however, that only 7 patients in the whole study received a stent, hence making the relevance of these data to current clinical practice (in which stent rates are up to 90% in some centers) unclear. In EPILOG,[46] 2792 patients undergoing urgent or elective PTCA were randomized to receive: (a) ReoPro bolus (0.25 mg/kg) followed by an infusion (0.125 mg/kg/min for 12 hours) in combination with standard dose heparin (100 U/kg or maximum 10,000 U); or (b) ReoPro bolus (0.25 mg/kg) followed by an infusion (0.125 mg/kg/min for 12 hours) in combination with weight-adjusted heparin (70 U/kg, maximum 7000 U); or (c) placebo bolus and infusion with standard dose heparin (100 U/kg or maximum 10000 U). Abciximab unequivocally reduced the risk of acute ischemic complications of PTCA in this population. In addition, the occurrence of significant hemorrhagic complications was reduced to that seen with heparin alone when abciximab was employed with weight-adjusted heparin (70 U/kg) (Table 8.4).

The third abciximab study, CAPTURE,[48] recruited 1265 patients with refractory unstable angina. In order to be included into the study, these patients underwent angiography, and those in whom PTCA was deemed suitable therapy were then randomized to receive either: (a) planned treatment with abciximab bolus (0.25 mg/kg) followed by an infusion (10 mg/min) for 8–24 hours prior to intervention plus 1 hour afterwards; or (b) placebo bolus and infusion. The composite endpoint was represented by the combination of 'death plus MI plus need for urgent intervention', and there was a significant reduction in the

endpoint at 3 months, 15.9% in the placebo group versus 11.3% in the abciximab group, $p = 0.012$. However, this outcome benefit was not preserved at the 6-month follow-up time point. There has been speculation that the disparate longer-term follow-up results between this and the EPIC study may be explained by the short post-procedure abciximab infusion time in CAPTURE.

The EPIC and EPILOG studies included only 7 and 382 patients in whom stents were implanted, respectively. The current stenting rates in the UK vary but run at over 90% in many centers, thus raising the suspicion that these studies were dealing with a different patient group at follow-up than the patients routinely treated in practice. Further data are therefore required to help establish whether the benefits of abciximab in patients undergoing balloon angioplasty only (POBA) are also available to a population of patients undergoing stent deployment. Recent publication of the EPISTENT study[47] has gone some way to answer this question, although not specifically in the context of unstable angina. EPISTENT recruited 2399 patients with ischemic heart disease and coronary anatomy suitable for PTCA. Approximately one third of the total study population comprised patients who had an acute coronary syndrome. The study randomized to three groups: (a) stent plus placebo; (b) stent plus abciximab; and (c) balloon only plus abciximab. Abciximab was administered as a bolus (0.25 mg/kg) up to one hour before intervention, followed by an infusion of 0.125 mg/kg/min for 12 hours. Again, the composite endpoint was represented by 'death plus MI plus need for urgent revascularization'. At 30 days, there was a significant reduction in endpoint frequency in both the abciximab groups when compared to the stent plus placebo group, with the stent plus abciximab group having the lowest rate of all (Table 8.5). Thus, in this heterogeneous group of patients, abciximab substantially improved the safety of coronary stenting procedures, and balloon angioplasty with abciximab is safer than stenting without abciximab. The contentious speculation arising from this study has, of course, been that there is an argument for treating all patients who undergo PTCA with abciximab![81] The more recent three-year outcome data have shown that the difference between the 'stent plus abciximab' and 'stent plus placebo' groups is maintained, but the advantage of 'balloon only plus abciximab' over 'stent plus placebo' is lost. The study does not, unfortunately, specifically address the question that we are asking, namely: does abciximab reduce the complication rate in coronary stenting procedures in patients with unstable angina? The current (circumstantial) evidence makes this highly likely, however. Most interventionists utilize abciximab in patients who are identified as being at 'high risk' according to currently defined risk stratification data.[69,82,83]

Future prospects

Intensive research is currently dedicated to improving outcome of percutaneous intervention in patients with unstable angina. Alterations in stent design and technology may attenuate the complication rates by such novel techniques as coating of the device with anticoagulants, IIb/IIIa receptor inhibitors etc. New technologies with which to remove thrombus from coronary arteries are currently being tested and will prove useful in this context if successful. Despite these and other

major advances in mechanical systems, it seems perfectly likely that outcome will be improved further when a more efficient system can be deployed in which high-risk patients are referred for, and receive, their definitive revascularization before they suffer a cardiac event.

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9

Myocardial Stunning

Aldo Rinaldi and Roger Hall

Introduction

Myocardial stunning has been defined as 'the mechanical dysfunction that persists after reperfusion despite the absence of irreversible damage and despite restoration of normal or near normal blood flow'.[1] Stunning represents an example of 'flow-function mismatching'. Stunned myocardium recovers spontaneously, a process which may take minutes or days depending on the severity of the causative ischemic insult. The precise mechanism of stunning remains unknown although it is thought to be a form of reperfusion injury.[2] It is likely that a combination of oxygen radical production and release during ischemia/reperfusion results in reversible damage to mechanisms of calcium transport and homeostasis which causes functional abnormalities of contraction and relaxation.[1]

Stunning has been shown to occur following brief and prolonged, regional and global ischemia and reperfusion in both isolated heart preparations and intact animal models. Evidence has been gathered over the past decade for the occurrence of stunning in man in a number of clinically important situations.[3] These include myocardial infarction (MI), unstable angina, coronary vasospasm, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass grafting (CABG) and exercise-induced ischemia in patients with stable coronary artery disease.

It is important to differentiate stunned myocardium from hibernating myocardium, a term created by Rahimtoola to describe a state of persistently reduced left ventricular (LV) function at rest because of chronically reduced coronary flow.[4] Hibernating myocardium by definition has the capacity to improve fully or partially with restoration of coronary flow following revascularization. It is thought to represent an adaptive response of the heart with down regulation of myocardial function secondary to chronically impaired flow, so called 'flow-function matching'.[5] Although hibernating myocardium by definition exists in the presence of reduced coronary flow, it is not thought to be a chronic ischemic state. Rather it is an adaptive metabolic state resulting from, and in essence preventing, ongoing ischemia. The underlying cause of chronic dysfunctional myocardium of this type remains elusive and at present there are no adequate longterm animal models of hibernation. Revascularization of hibernating myocardium improves both global and regional LV function and significant improvements in ejection fraction (EF) have been demonstrated in up to one third of patients undergoing surgery for this indication with normalization of EF in approximately one quarter.[6]

Clinical occurrence

Stunning has been shown to occur in man in a number of clinically important situations involving a cycle of ischemia followed by recovery from ischemia (Table 9.1).

Myocardial infarction

If reperfusion occurs while MI is developing, the reperfused area becomes stunned, as it has been severely ischemic but has the potential for functional improvement. Reperfusion may occur either spontaneously or as a result of therapeutic measures (thrombolysis and/or PTCA). Significant abnormalities of systolic and diastolic myocardial function occur following reperfusion in this situation, with a prolonged time course because the ischemic insult is a very severe one. Studies have shown that recovery of stunned myocardium is relatively slow, and may take 7–10 days.[7]

Cardiac surgery

Cardio-pulmonary bypass for cardiac surgery produces prolonged global ischemia and is thought to result in clinically relevant stunning of sufficient severity to alter the type of clinical care required. Several clinical reports have demonstrated transient LV dysfunction post-CABG which usually resolves within 24–48 hours of surgery and is independent of hemodynamic alterations. Similarly cardiac transplantation involves prolonged global ischemia and is also thought to result in myocardial stunning.[8]

- Myocardial infarction
- Post-CABG
- PTCA
- Unstable angina
- Variant angina
- Exercise-induced ischemia

Table 9.1
Clinical occurrence of stunned myocardium.

PTCA

PTCA produces regional myocardial ischemia followed by reperfusion, but the duration of coronary artery occlusion is relatively short. Most studies of uncomplicated PTCA have failed to show any significant degree of systolic stunning, although prolonged diastolic abnormalities have been demonstrated.[9]

Unstable angina

In unstable angina, the duration and severity of ischemia is very variable. Significant abnormalities of LV function, with a timecourse consistent with stunning, have been demonstrated.[10] It should be noted that these variations of function were assessed without simultaneous measurement of perfusion. It is therefore possible that they were secondary to a reduction in myocardial blood flow and so might represent silent ischemia or myocardial hibernation.

Variant angina

The evidence for the occurrence of stunning in variant angina is restricted to case reports and similarly the ischemic insult may not be severe enough to cause significant functional abnormalities.

Effort angina

Early echocardiographic studies demonstrated regional wall motion abnormalities (WMAs) which persisted for up to 30 minutes post-exercise.[11] Radio nuclide abnormalities of diastole have been shown to persist for up to 48 hours following exercise.[12] Reversible systolic dysfunction which persisted for up to 1 hour, and diastolic dysfunction for up to 4 hours following exercise-induced ischemia, has been demonstrated in up to 80% of patients with severe coronary artery disease.[13] Simultaneous measurement of contractile function and flow (using 2D echocardiography and T_c-sestamibi respectively) has shown that these functional changes persist when myocardial perfusion has normalized, which proves that the abnormalities are due to myocardial stunning.[14]

Can stunning produce chronic LV dysfunction?

It has been suggested that repeated episodes of myocardial stunning may produce cumulative and even chronic LV dysfunction.[15,16] It is possible that patients with coronary artery disease suffer from persistent LV dysfunction as a result of repeated episodes of ischemia caused by daily activities. Repeated episodes of this type may explain ischemic cardiomyopathy and may also account for at least some of what has previously been called 'hibernation'. Ambulatory electrocardiographic studies have suggested that such patients may experience from ten to at least twenty episodes of ischemia daily and, under such conditions, the myocardium may become chronically depressed. Further support for this hypothesis is provided by the fact that many dysfunctional segments thought to be hibernating have been demonstrated using positron emission tomography (PET) to have normal resting blood flow.[15] In an echocardiographic study, two repeated episodes of exercise-induced ischemia were shown to have a cumulative effect on LV systolic and diastolic function (Fig. 9.1).[16] The effect of ischemia on LV function in this study was however highly dependent on the time interval between ischemic insults.

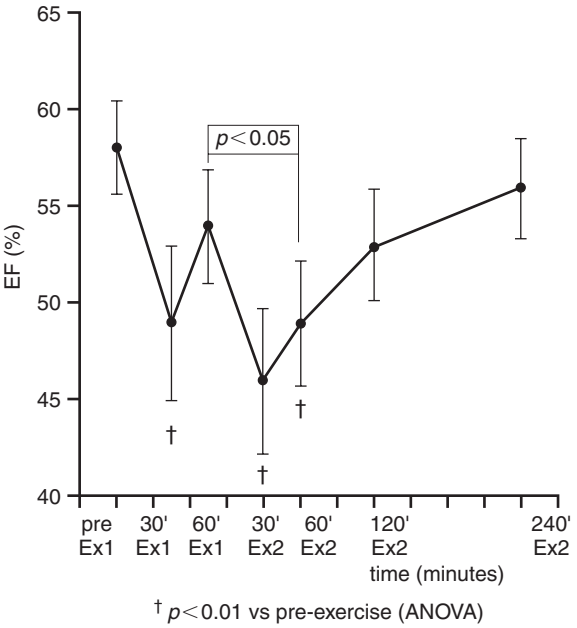

Figure 9.1
Effect of repeated exercise-induced ischemia. Ischemia was repeated at 60 minutes on global ejection fraction (EF) in 11 patients who exhibited prolonged wall motion abnormalities consistent with stunning. EF was significantly more depressed at 60 minutes after the second exercise (Ex2) compared to 60 minutes post Ex1, which suggests a cumulative effect of repetitive ischemia on LV function. Data reproduced from Rinaldi et al.[16]

Diagnosis

In acute situations where stunning is important, e.g. post-MI, the identification of viable but stunned myocardium may have significant prognostic implications.[7] The stunned myocardium can be expected to improve over the following days and every effort should be made to support the patient whilst recovery occurs.

Diagnostic techniques can be divided broadly into those that assess metabolism, perfusion and cellular integrity of viable myocardium and those that demonstrate its functional reserve (Table 9.2). The two most widely available and employed techniques are nuclear perfusion imaging and low-dose dobutamine stress echocardiography (LDDE). Myocardial perfusion imaging identifies viable stunned myocardium, as tracer uptake requires adequate perfusion, cellular integrity and metabolic function. Impaired but recoverable myocardium possesses a functional reserve which allows it to be temporarily recruited into action, whereas scar tissue cannot. This difference can be used as a diagnostic tool. Low dose infusion of dobutamine (5–10 μg/kg/min) results in recruitment of dysfunctional stunned myocardium and the resulting improvement can be assessed using two-dimensional echocardiography. LDDE has been shown to be a reliable method of identifying viable myocardium due stunned myocardium. PET can accurately identify stunned viable myocardium but the lack of availability of this technique makes it impractical as a first measure.

- Perfusion and cellular integrity
  - Thallium imaging (rest/stress redistribution/re-injection)
- Demonstration of functional reserve
  - Nitrates
  - Low-dose dobutamine echocardiography (LDDE)
- Metabolism/perfusion
  - PET

Table 9.2
Identification of viable myocardium.

Treatment

The treatment of stunning can be divided into that which occurs in the acute situation, usually when the patient is hospitalized, and the chronic situation which may be encountered in daily life. Although stunning is by definition reversible, it is likely to cause significant morbidity and mortality as a result of hemodynamic instability during the period of recovery from ischemia. In the acute settings in which stunning tends to occur, e.g. following MI or CABG, intensive pharmacologic and or mechanical circulatory support may be required. Decisions on whether to perform revascularization or on duration of aggressive treatment may be affected. Most positive inotropes have been found to be beneficial in these clinical situations: the standard treatments of such LV dysfunction are inotropic therapy and after-load reduction with vasodilators. Use of inotropic therapy is not without risk because it increases myocardial oxygen demand and arrhythmias, which are both undesirable side-effects in these settings. Inotropic therapy also requires intensive monitoring and invasive procedures. In these acute situations, the prevention of stunning before it produces hemodynamic instability is an attract-

ive aim as it may also facilitate a quicker recovery of myocardial function. Importantly, if myocardial stunning and hibernation share a common mechanism and if hibernating myocardium may actually reflect chronic repeated stunning, then therapies to prevent stunning would be important in preventing significant LV dysfunction on a regular and cumulative basis in patients with CAD.

Potential therapeutic agents

A variety of pharmacologic approaches are being explored (Table 9.3). The two most promising treatments are antioxidants, which prevent free radical-mediated damage, and the calcium antagonists, which probably reduce the calcium overload implicated in the pathogenesis of stunning. In animal models, a number of classes of drugs have been shown to attenuate myocardial stunning and may offer potential benefit in the treatment of myocardial stunning in man. These drugs include antioxidants, calcium antagonists, ACE inhibitors and other less well-established agents.

- Antioxidants
- Calcium antagonists
- ACE inhibitors
- K_{ATP} channel openers
- Adenosine
- Magnesium
- Na^+/H^+ inhibitors
- Nitric oxide

Table 9.3
Potential therapeutic agents in myocardial stunning.

Antioxidants

The key role that oxygen-derived free radical species are thought to play in the pathogenesis of myocardial stunning would suggest that antioxidant therapies directed against their production would be beneficial. Experimental evidence in animal models suggests that antioxidants attenuate stunning if administered before reperfusion and their potential benefit would appear significant.[17] Free radical production begins with the onset of ischemia but the bulk of production is during early reperfusion. Benefit from antioxidants is only seen when they are given either before the onset of ischemia or just prior to reperfusion. Therapy following reperfusion does not attenuate stunning.[18] In man, experience with antioxidant therapies are confined to the setting of prolonged global ischemia and reperfusion in the context of CABG. Allopurinol by blocking xanthine oxidase (one of the major pathways for free radical generation) reduces superoxide radical production and has been shown to improve post-operative LV function.[19] A beneficial effect on post-operative LV function after CABG has been reported following pre-treatment with vitamin E. However because of its lipophilicity, pre-treatment for 2 weeks was necessary to achieve adequate tissue levels.[20]

Calcium antagonists

Calcium overload is felt to be important in the pathogenesis of myocardial stunning and accordingly calcium antagonists which are able to prevent this have been shown to attenuate stunning. In animal models, pre-treatment with the calcium antagonists verapamil, diltiazem and nifedipine attenuates myocardial stunning.[21] The potential for calcium antagonists to attenuate stunning when administered

post-reperfusion is controversial. This setting has important clinical implications in the thrombolytic era. In support of a late benefit from calcium antagonists, functional improvement of stunned myocardium was shown with verapamil administered following reperfusion, but the benefit was not as marked as when given prior to reperfusion.[21] There appears to be a short but critical time window during early reperfusion when calcium overload occurs and treatment with calcium antagonists are beneficial. However, later treatment may actually worsen contractile function.

The beneficial effect of calcium antagonists on myocardial stunning has been extended to humans in certain settings. In the context of coronary angioplasty, the effect of pretreatment with nifedipine, nisoldipine and nitrates to patients with exercise-induced angina and at least 80% left anterior descending (LAD) artery stenosis was studied.[22] Post-ischemic LV systolic and diastolic dysfunction assessed by serial echocardiography was significantly improved by both calcium antagonists (greater for nisoldipine than nifedipine), whereas nitrates had no benefit. It should be noted that these studies involved PTCA with prolonged inflations (5 ± 1 minutes) and may not therefore be applicable to conventional PTCA. Calcium antagonists have also shown a benefit on stunned myocardium in the context of thrombolysis.[23] In a recent study in man, systolic and diastolic dysfunction post-exercise was attenuated by sublingual nifedipine but not nitroglycerin administered at peak exercise.[24] In this study, however, there were favourable changes in hemodynamics with nifedipine which may have contributed to its beneficial effect by a reduction in cardiac work which might have reduced ischemia and indirectly the degree of stunning.

In a double-blind randomized study of 24 males with chronic stable angina and normal LV function, exercise-induced stunning assessed with echocardiography was attenuated by the long-acting calcium antagonist amlodipine when compared to an equivalent anti-ischemic dosage of a long-acting nitrate.[25] In this cross-over study, stunning occurred more often in patients whilst receiving nitrate than amlodipine (82% vs 48%), despite comparable amounts of ischemia as measured using perfusion imaging (Fig. 9.2; Table 9.4).

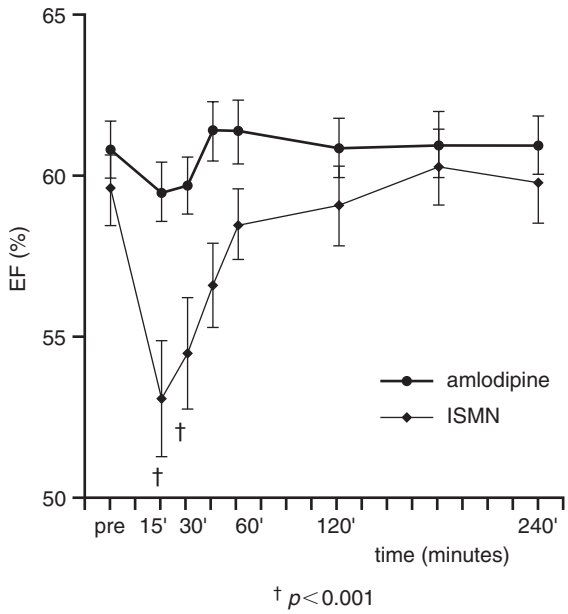

Figure 9.2
Exercise-induced ischemia on amlodipine and isosorbide mononitrate (ISMN). Changes in global ejection fraction following exercise-induced ischemia on amlodipine and ISMN in 24 patients with CAD. The effect of ischemia on LV function is lessened whilst patients are taking amlodipine, despite a comparable ischemic burden. Data reproduced from Rinaldi et al.[25]

	15 minutes post		*30 minutes post*		
	Amlodipine	*ISMN*	*Amlodipine*	*ISMN*	p *value*
• SF (%)	3.7 (0.42)	3.1 (0.49)	3.6 (0.32)	3.2 (0.5)	0.001
• EF (%)	59.5 (4.9)	53.1 (7.8)	59.7 (5.4)	54.4 (8)	0.001
• IRP (msecs)	88.0 (15.0)	107.0 (18.0)	94.0 (15.0)	106.0 (14.0)	0.018

Data reproduced from Rinaldi et al.[25]
SF = shortening fraction; EF = ejection fraction; IRP = isoudonic relaxation period.

Table 9.4
The effect of amlodipine on post-exercise stunning

This is the first randomized trial to show a beneficial effect of calcium antagonists (or any other treatment) on exercise-induced stunning. This benefit may relate to a prevention of the calcium overload implicated in the pathogenesis of stunning. This finding may have important therapeutic implications, since it is likely that stunning occurs following episodes of ischemia during everyday life which could result in prolonged episodes of LV dysfunction.

The mechanism by which calcium antagonists attenuate myocardial stunning is unclear, although several different possibilities exist. Calcium antagonists possess hemodynamic and coronary vasodilatory effects, both of which lessen ischemia. The benefit of calcium antagonists in myocardial stunning could be explained by favourable hemodynamic alterations, as any intervention which decreases the severity of the initial ischemic insult will attenuate stunning.[26] Their effect on slow calcium channels suggests a direct cardioprotective effect of calcium antagonists on 'stunned' myocytes as a result of modulation of intracellular calcium fluxes. Whilst producing no significant hemodynamic effects, very small doses of intracoronary nifedipine administered following reperfusion have been demonstrated to attenuate stunning in the canine model.[27] Apart from hemodynamic and calcium flux alterations, the beneficial effects of calcium antagonists on myocardial stunning may be due to a free radical scavenging effect. The calcium antagonists nifedipine, verapamil and diltiazem have either free radical scavenging properties or inhibit the peroxidation of membrane lipids.[28]

Angiotensin converting enzyme (ACE) inhibitors

ACE inhibitors are known to be of benefit when administered in the context of acute myocardial infarction via manipulation of the renin angiotensin system (RAS). It has been suggested that acute ischemia results in activation of the RAS that may exacerbate ischemic injury and that ACE inhibitors may be beneficial in the context of myocardial stunning as a result. ACE inhibitors would be expected to

attenuate myocardial stunning indirectly by virtue of their hemodynamic effects, resulting in reduced afterload and increased coronary flow. In addition, it has been proposed that ACE inhibitors may possess a direct beneficial effect on stunned myocardium which may be mediated via bradykinin,[29] prostaglandins,[30] or free radical scavenging.[31]

Experimental evidence supports a beneficial effect on myocardial stunning from a variety of ACE inhibitors. In isolated rat hearts subjected to reversible ischemia and reperfusion, ramipril[32] and captopril[33] have been shown to attenuate post ischemic myocardial contractile abnormalities and similar results have been shown in the intact animal.

At present there is no evidence that ACE inhibitors attenuate stunning in man as no studies have been performed. It has been suggested that the beneficial effect of ramipril seen in the AIRE study may be in part related to an effect on myocardial stunning.[34] An early reduction in mortality was seen at a time when we would expect stunning to be occurring, however this is speculative. In addition to their other properties, ACE inhibitors appear to offer a potential therapy against myocardial stunning in man although much experimental work will be required to elucidate this.

K_{ATP} channel openers

K_{ATP} channels (potassium channels) are a diverse group of ion channels existing in cardiac myocytes which regulate cellular excitability. K_{ATP} channel opening is stimulated by decreasing ATP levels. In most cells under normoxic conditions, the amount of ATP present means that these channels are usually closed. K_{ATP} channels open during ischemic stress, which results in cellular hyperpolarization and decreased cellular excitability. The exact function of K_{ATP} channels is unknown, but it seems they play a key role in hypoxia when ATP is depleted. Their major function has been proposed to be myocyte preservation during ischemia as a consequence of preconditioning.[35]

K_{ATP} channel openers are a group of drugs with vasodilator, antianginal, antihypertensive and cardioprotective action. Nicorandil is an antianginal drug which has both nitrate-like and K_{ATP} opening properties and is the first clinically available drug with these latter properties. In animal models, both nicorandil[36] and the pure K_{ATP} channel openers[37] have been shown to attenuate myocardial stunning. The ability of glibenclamides (which antagonize the effects of K_{ATP} openers) to abolish the beneficial effects of K_{ATP} openers suggests a direct mechanism for their observed action. It is postulated that K_{ATP} channel opening shortens the action potential duration, thus preventing or attenuating calcium entry into the cell during early ischemia and reperfusion, thereby preventing harmful calcium overload.

Adenosine

Adenosine is an endogenous cardiac nucleotide produced primarily from the degradation of adenosine triphosphate (ATP). Ischemia results in increased levels of adenosine which, via coronary vasodilation, allows more oxygen to be delivered to the heart to meet demand. Endogenous adenosine plays an important role in the protection of the myocardium against post-ischemic stunning, although the mechanism for this action is not clear at present. Administration of exogenous adenosine or therapies which augment endogenous adenosine initiated during this period and prior to reperfusion represent a possible treatment for myocardial stunning. A new class of com-

pounds known as adenosine regulating agents which increase endogenous adenosine have also shown benefit in animal models of stunning.[38]

Magnesium

Magnesium is a peripheral and coronary vasodilator, with antiarrythmic and antiplatelet properties. Adding magnesium to potassium-based cardioplegic fluid improves postischemic aortic flow by combating magnesium loss during ischemia.[39] This has led to the introduction of the St Thomas cardioplegic solution which is in world-wide use. In isolated rabbit hearts subjected to global ischemia, a perfusate supplemented with magnesium and a depleted calcium content was able to attenuate stunning.[40] In man, the effect of magnesium on myocardial stunning has been studied in the context of reperfusion following MI. Early studies in acute MI demonstrated a reduction in mortality and arrhythmias in patients treated with intravenous magnesium. In the LIMIT-2 trial, over 2000 patients with suspected acute MI were randomized to receive either a magnesium infusion or placebo.[41] In the magnesium-treated group, there was a significant reduction in all cause mortality at 1 month of 24%. A reduction in acute heart failure on the CCU of 25% was also felt to be due to a beneficial effect on stunned myocardium. The ISIS 4 study, which included 58 000 patients, failed to demonstrate a benefit from magnesium infusion in respect to mortality.[42] It should be noted however that in LIMIT-2, magnesium was infused significantly earlier than in ISIS 4 and was likely to be present at the time of reperfusion. The timing of treatment of myocardial stunning is critically important and previous studies have shown that the therapeutic window of magnesium is confined to the first 1–2 minutes of reperfusion.[43] This may explain the differing results, although further analysis of ISIS 4 results indicated no benefit, even among the 10 252 patients randomized within 3 hours of the onset of symptoms.[44]

Na^+/H^+ exchange inhibitors

The sodium-hydrogen ion (Na^+/H^+) exchange system is the major pathway for regulation of intracellular pH in vertebrate cells and represents the main mechanism for restoration of intracellular pH following ischemia. Na^+/H^+ exchange itself is thought to play a contributory role in the pathogenesis of myocardial stunning via the nitrogen calcium (Na/Ca) exchanger causing calcium influx and overload. In view of this proposal, Na^+/H^+ exchange inhibitors which block sodium entry into the cell would be expected to have a beneficial effect on myocardial stunning and this has been shown in animal models.[45]

Nitric oxide

Nitric oxide (NO) is a potent vasodilator released by the coronary endothelium with antiplatelet and antineutrophil properties. Numerous agents including L-arginine, superoxide dismutase and the prostacyclin analogues have been shown to preserve NO production by the coronary endothelium during ischemia and reperfusion. At present the evidence concerning NO in stunning is conflicting and restricted to the settings of prolonged ischemia and reperfusion. These settings probably result in a degree of myocardial necrosis as well as stunning. Importantly the beneficial effect of NO donation on myocardial protection following prolonged ischemia and reperfusion is attributed to antineutrophil

properties[46] and it is accepted that neutrophils are not implicated in the pathogenesis of stunning.

Therapies with no direct effect

There are several therapies which have not been shown to be of benefit in myocardial stunning, including nitrates and beta-blockers. These merit discussion as they are important cardiovascular medications in the treatment of coronary artery disease. Any treatment which decreases ischemia is able to indirectly decrease stunning by virtue of lessening the ischemic insult, the magnitude of which dictates the degree of stunning. There is however no conclusive evidence that nitrates have a direct beneficial effect on stunned myocardium as opposed to their well-known anti-ischemic properties. Similarly beta-blockers have not been shown to have any significant benefit on stunning in animal models.[47]

Summary

Stunned myocardium is a reversible form of LV dysfunction which occurs in a variety of clinical settings involving ischemia. Identification of clinically available therapeutic strategies that attenuate stunning, and therefore lessen the impact of ischemia on LV function, may represent an important step in improving the medical management of patients with coronary artery disease. It has been suggested that repeated episodes of stunning may actually be the cause of chronic LV dysfunction currently termed as 'hibernating'. If this was so, then pharmacologic agents which prevent stunning could also represent a potential treatment of chronic LV dysfunction in patients with CAD.

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10

Ischemic Preconditioning: from Bench to Bedside

Ali Dana and Derek M Yellon

Introduction

In recent years there has been considerable interest in the pathophysiology of myocardial ischemia-reperfusion injury. The possibility that the heart may be rendered more resistant to the damaging effects of ischemia is an attractive therapeutic goal. This has been driven partly by epidemiologic data that confirm the place of coronary artery disease as the leading cause of death in the developed world. Over the past ten years, the widespread adoption of thrombolytic therapy and invasive, revascularization procedures have revolutionized the management, and improved the prognosis, of acute myocardial infarction (MI). However, other than this rapid and complete restoration of blood flow to the ischemic myocardium, there have been no therapeutic interventions available to enhance myocardial tolerance to ischemia and counter the threat of myocardial necrosis. In this context, interventions aimed at modifying the symptoms of angina, such as beta-blockers, calcium antagonists and nitrates, have met with little success.

However, adaptive changes may occur in myocardium, following brief periods of sublethal ischemia, which confer protection against subsequent lethal ischemic injury. For example, the phenomenon of ischemic preconditioning has been shown to provide the myocardium with the most powerful means of delaying MI known to date.[1] Other adaptive mechanisms include the longterm development of coronary collateral vessels,[2] and myocardial hibernation.[3] This chapter reviews ischemic preconditioning and how it might lead to the development of new pharmacologic approaches to myocardial protection as well as allowing a re-appraisal of the overall management of acute ischemic syndromes.

Experimental evidence

Until the mid-1980s, it had been generally assumed that repetitive short periods of myocardial ischemia would have a cumulative deleterious effect, resulting in progressive cell necrosis. In 1986, Reimer and colleagues conducted experiments which were designed to explore the relative contribution of high energy phosphate depletion and catabolite accumulation to lethal cell injury in the canine myocardium.[4] However, unexpected results came to form the basis of the concept of endogenous myocardial adaptation to sublethal ischemia. The experimental model involved repetitive brief episodes of regional myocardial ischemia in the anesthetized dog. Following the initial period of ischemia, there

was surprisingly no further reduction in the ATP levels during subsequent similar ischemic challenges. The investigators went on to examine the possible protective effects of brief sublethal ischemia in the same model.[1] Four 5-minute coronary occlusions, separated by 5 minutes of reperfusion prior to 40 minutes of sustained ischemia, resulted in a 75% reduction in infarct size compared with a control group. Reimer and colleagues termed this phenomenon 'ischemic preconditioning' and concluded that the multiple anginal episodes that often precede MI in man may delay cell death after coronary occlusion, and thereby allow for greater salvage of myocardium through reperfusion therapy.[1]

These original findings have stimulated extensive research in order to identify further the characteristics of this phenomenon, to elucidate underlying cellular mechanisms responsible for these protective effects and to establish whether brief antecedent ischemia can also effectively protect the human heart. It is now known that, apart from timely reperfusion, ischemic preconditioning is the most powerful and reproducible experimental means of myocardial protection. It has been demonstrated in every animal species studied, including dogs,[5] rabbits,[6] rats,[7] mice,[8] guinea pigs[9] and pigs.[10] There is also recent evidence that the human myocardium can be preconditioned and that ischemic preconditioning may occur as part of some naturally occurring ischemic syndromes.[11]

In addition to enhanced tolerance to lethal cell injury, it has been furthermore recognized that preconditioning ischemia is protective against other endpoints of ischemia-reperfusion injury, including post-ischemic contractile dysfunction,[12] and ischemia- and reperfusion-induced ventricular arrhythmias.[13] Evidence suggests moreover that, distinct from necrotic cell death, the irreversible cellular injury that results from cardiomyocyte apoptosis (programmed cell death) during ischemia and reperfusion may also be attenuated by brief antecedent ischemia.[14,15] Interestingly, reports from a number of centers indicate that brief antecedent episodes of ischemia of remote, non-cardiac tissue are also capable of preconditioning the heart. This phenomenon has been termed 'preconditioning at a distance'.[16] Studies show significant cardiac protection in rat and rabbit models induced by prior transient episodes of renal, mesenteric and skeletal muscle ischemia.[17–19]

The temporal characteristics of the protective effects of ischemic preconditioning have also been described. It appears that the protection afforded by preconditioning ischemia is apparent within minutes of the preconditioning stimulus, but wanes dramatically after 1–2 hours.[20,21] This protection can however be re-established if a second preconditioning stimulus is instituted immediately before the sustained occlusion.[22,23] It was reported in 1993 that, if the intervening period of reperfusion between the preconditioning and the test ischemia is extended to 24 hours, a delayed phase of myocardial protection is induced.[24,25] Although this is not as powerful as the early phase, the protection is more prolonged and lasts up to 72 hours.[26] This delayed phase of resistance to ischemic injury has been termed the 'second window of protection' (SWOP),[27] and is distinguished from early or 'classic' preconditioning (Fig. 10.1). It is likely that these two forms of adaptation have different underlying mechanisms, although they share the same trigger of transient ischemia.

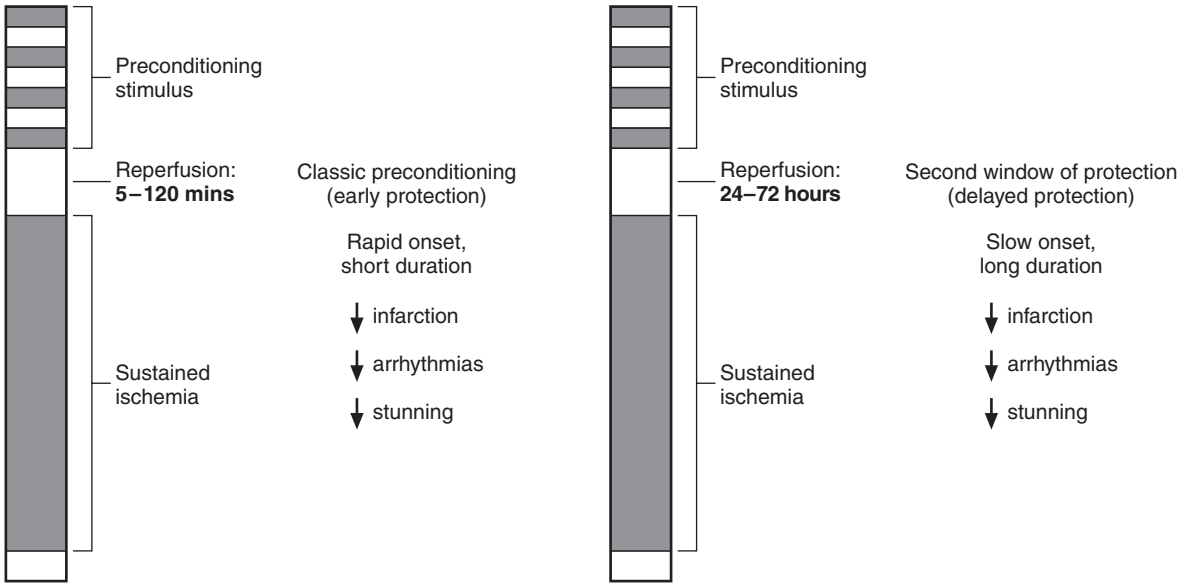

Figure 10.1
The two phases of preconditioning. The ischemic preconditioning stimulus consists of one or more episodes of transient ischemia, followed by an intervening period of reperfusion, before the sustained ischemic insult.

Classic ischemic preconditioning

The mechanisms that underlie early preconditioning are not completely understood. A number of possible mechanisms initially suggested to contribute to the protective effects of preconditioning have however been ruled out. It is known, for instance, that the enhanced tolerance conferred by preconditioning ischemia is not explained by simple recruitment of collateral vessels, as the protection is present for any degree of collateral flow in dogs.[1] Furthermore, preconditioning has been shown to be protective in animal models with little or no collateral flow, such as the rat,[7] rabbit[6] and pig heart,[10] and is also evident in isolated hearts subjected to global ischemia.[28] This latter model of preconditioning, the isolated buffer perfused heart, also excludes the necessity of blood-borne factors for preconditioning. Another early suggestion, that the stunning effect of the brief periods of preconditioning ischemia reduces the metabolic demands of the myocardium during sustained ischemia, so resulting in a smaller infarct size, has also been dismissed.[29]

A vast amount of research strongly suggests that preconditioning-induced cardioprotection is a receptor-mediated phenomenon. In other words, it is believed that brief episodes of ischemia result in the release of a number of endogenous autocrine and

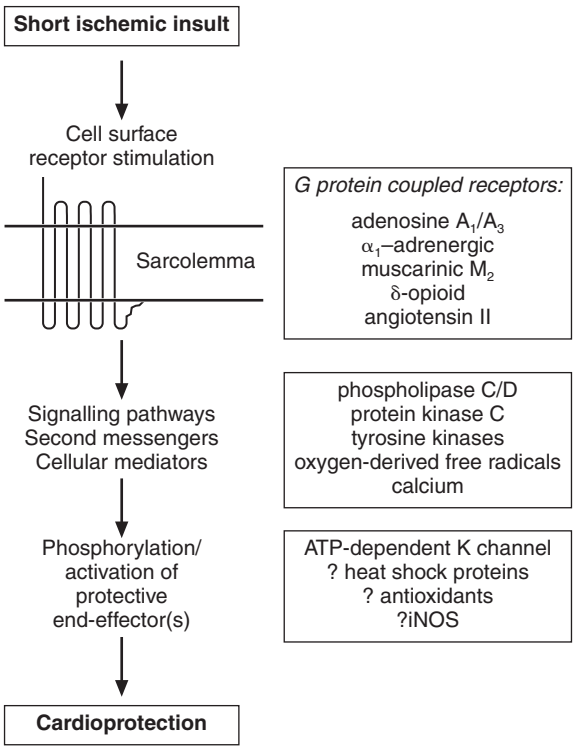

Figure 10.2
Cellular mechanisms proposed in the cardioprotection induced by ischemic preconditioning.

paracrine substances that act on one or more receptors on the myocyte membranes, thereby initiating intracellular signal transduction pathways. These in turn activate one or more effector proteins which ultimately render the myocytes resistant to subsequent lethal ischemic injury (Fig. 10.2).

Triggers

Various models of preconditioning in different species have implicated the involvement of substances such as adenosine,[6] acetylcholine,[30] catecholamines,[31] angiotensin II,[32] bradykinin,[33] endothelin[34] and opioids.[35] It has been suggested that these multiple triggers may interact in producing the final cardioprotective effects of preconditioning, and it is possible that sufficient 'redundancy' exists to allow for cardioprotection by other mechanisms when any individual trigger is inhibited.[33] This hypothesis remains to be proven and the relative importance of these triggers seems to be dependent on the species and the endpoints of protection studied. Adenosine, for example, seems to be the main trigger in the rabbit,[6] dog,[36] and pig myocardium.[37] In the rat heart, however, the role of adenosine in mediating cardioprotection remains controversial[7,38] and noradrenaline has been found to be the important trigger.[31] This discrepancy could have resulted from the fact that, following a period of ischemia, the interstitial concentration of adenosine in the rat heart is three- to four-fold higher than that in the rabbit myocardium and higher concentrations of selective antagonists are required to abolish the protective effects of preconditioning.[39]

Mediators

A number of these triggers, such as adenosine, noradrenaline, acetylcholine and bradykinin are coupled to pertussis toxin-sensitive inhibitory G proteins (G_i). It has been proposed that activation of these G_i protein-coupled receptors by various ligands in turn results in activation of a complex intracellular signaling cascade that involves a number of protein kinases. Protein kinase C (PKC) is a family of at least twelve related isoenzymes known to participate in the regulation of ionic homeostasis, vascular tone, myocyte contractility and many other cellular processes.[40,41]

PKC is thought to play a central role in the signaling cascade that results in phosphorylation of specific target proteins.[42]

A number of recent studies have supported this hypothesis, which was originally proposed by Downey.[43] Ischemic preconditioning has been blocked by pretreatment with specific PKC inhibitors[44,45] and the substitution of preconditioning ischemia with PKC activators mimics the infarct-limiting effects of ischemic preconditioning.[45] The specific PKC isoenzyme/s activated during preconditioning ischemia is/are not known, although involvement of PKC-delta and -epsilon has been proposed.[46,47]

It is also likely that other protein kinases, in parallel with or following activation by PKC, may play a role in classic ischemic preconditioning. Evidence suggests that the activity of tyrosine protein-kinase may be a crucial step in this signaling cascade since genistein, a selective tyrosine kinase inhibitor has been shown to abolish the protective effects of preconditioning in the rabbit heart.[48] The relative importance and positions of PKC, tyrosine kinase and other kinases in the signal transduction pathway of ischemic preconditioning are currently under further investigation.

End-effectors

One possible end-effector for the protective effects of ischemic preconditioning is the ATP-sensitive potassium channel (K_{ATP}). It was originally hypothesized that opening of sarcolemmal K_{ATP} channels results in a repolarizing current that reduces the duration of the cardiac action potential, so leading to reduced calcium entry to the myocyte.[49] This in turn reduces cardiac workload and enhances myocardial viability. The evidence in support of a role for K_{ATP} channels in ischemic preconditioning comes from studies in rats,[35] rabbits,[50] dogs,[51] pigs[49] and man[52] where blockade of these channels has abolished the protective effects of classic preconditioning. Pharmacologic activation of K_{ATP} channels with bimakalim however mimics ischemic preconditioning.[53] Furthermore, PKC has been shown to activate K_{ATP} channels in human and rabbit ventricular myocytes[54] and a synergistic action of adenosine and PKC on K_{ATP} channels and shortening of action potential duration has been reported.[55]

More recent work indicates that abbreviation of action potential duration may not be necessary for the protection from preconditioning and K_{ATP} channel openers.[56,57] In addition, K_{ATP} channel openers and ischemic preconditioning have been shown to be protective in models using unstimulated cardiac myocytes in which action potential duration should not be a factor.[58] This has prompted investigation into the role of K_{ATP} channels in other cell membranes, such as the mitochondrial K_{ATP} channel, in mediating ischemic preconditioning. Diazoxide, a potent opener of mitochondrial K_{ATP} with weak actions on sarcolemmal K_{ATP}, has been shown to protect isolated rat hearts against ischemic contracture and to improve post-ischemic functional recovery.[59] These effects were shown to be independent of action potential duration and were reversed by K_{ATP} blockers glibenclamide and 5-hydroxydecanoate. Similarly, in a model of simulated ischemia in intact rabbit ventricular myocytes, diazoxide reduced the rate of cell death to approximately 50% of that in controls.[60] Moreover, mitochondrial K_{ATP} channels seem to be modulated by PKC, since direct activation of this enzyme with the phorbol ester PMA both accelerates and augments the mitochondrial oxidation induced by diazoxide.[61] Further studies are warranted to

characterize the role of the mitochondrial K_{ATP} channel and the mechanisms by which opening of these channels may protect the ischemic myocardium.

Delayed preconditioning (second window of protection)

The delayed phase of myocardial protection following preconditioning ischemia was described more recently and its investigation is therefore at an earlier stage. This delayed enhanced tolerance to lethal ischemia was originally demonstrated in the rabbit[24] and in a canine model of myocardial infarction[25] 24 hours following brief cycles of regional myocardial ischemia. Further studies in rabbits,[62,63] dogs,[64] and rats[65] have since confirmed these original findings. In addition to enhanced tolerance to lethal ischemic injury, more recent evidence suggests that delayed preconditioning confers protection against other endpoints of ischemia-reperfusion injury, including ischemia and reperfusion-induced ventricular arrhythmias,[66] and post-ischemic myocardial dysfunction (stunning).[67,68] The delayed protective effect of preconditioning has also been demonstrated in vitro, using isolated cardiomyocytes subjected to simulated ischemia or hypoxia.[69,70]

The temporal profile of the delayed phase of myocardial protection following ischemic or pharmacologic preconditioning has recently been described for various indices of ischemia-reperfusion injury. The 'second window of protection' against myocardial necrosis in the rabbit extends between 24–72 hours following preconditioning ischemia,[26] a timecourse that closely parallels that of late preconditioning against stunning in conscious pigs, reported by Bolli and colleagues.[71] Although the protection against reperfusion-induced ventricular fibrillation is completely lost by 48 hours following rapid ventricular pacing in the dog,[72] there is evidence for protection against other arrhythmic indices up to 72 hours. The sustained nature of the delayed cardioprotection observed following preconditioning confers greater potential clinical relevance compared to the transient classic preconditioning.

The mechanisms underlying delayed preconditioning are not completely understood. Increasing evidence suggests that, similar to classic preconditioning, a number of mediators released during the preconditioning ischemia can trigger the protective signaling pathway. We have shown that transient adenosine A_1 receptor activation with selective agonists induces a delayed and sustained protection against infarction 24–72 hours later in the rabbit,[73–75] and in rat[76] myocardium. Conversely the delayed protective effects of preconditioning are abolished by pretreatment with adenosine-receptor blockers.[62] Meng et al described delayed cardioprotection against post-ischemic myocardial dysfunction in the rat 4–72 hours following transient α_1-adrenoceptor activation with norepinephrine, which was completely abolished by pretreatment with prazocin, an alpha-1-adrenoceptor antagonist.[77]

As with classic preconditioning, the specific trigger involved may be dependent on the species and the endpoint studied. For instance, no role has been demonstrated for adenosine receptors in the mechanism of delayed preconditioning against stunning in either the rabbit or the pig model.[67,68] Evidence from Bolli and colleagues has implicated a role for nitric oxide as both a trigger and a potential mediator of this form of protection.[79] Similarly, nitric oxide seems to be involved in mediating

the delayed cardioprotection against ventricular arrhythmias,[66,80] while the role of adenosine receptors in mediating this form of delayed protection has not been investigated.

As with classic preconditioning, there is growing evidence for an intermediate role for PKC in the signal transduction pathway of delayed preconditioning. PKC inhibition prior to preconditioning ischemia abolishes the cardioprotective effects at 24 hours in the rabbit model of infarction[81] and in the rabbit stunning model.[82] Alternatively, direct activation of PKC with a diacylglycerol analog results in enhanced tolerance to myocardial ischemia-reperfusion 24 hours later.[83] Furthermore, there is recent evidence for a crucial role for tyrosine kinase activation in this signaling cascade, since genistein administered prior to ischemic preconditioning abolishes delayed cardioprotection.[84] The involvement of both PKC and tyrosine kinase has also been demonstrated in mediating delayed cardioprotection in rabbits following pharmacologic preconditioning with the selective adenosine A_1 agonist CCPA.[75] The relative positions of PKC, tyrosine kinase and other protein kinases in the signaling pathway, and their possible interactions with membrane channels or protein synthesis are currently under investigation.

The final effectors of the delayed protection conferred by preconditioning are not known. As part of the cell-stress response to ischemia, sublethal ischemia results in the production of many new gene-products, such as proto-oncogenes, intracellular antioxidant enzymes, heat shock proteins and other regulatory proteins, as well as post-translational modification of such proteins.[85] Furthermore, the delayed appearance and subsequent duration of the second window of protection is consistent with involvement of new protein synthesis and degradation. Associations have been reported between the appearance of such cytoprotective proteins and late cardioprotection. Kuzuya et al[25] and Hoshida et al[86] reported that the infarct limitation observed in the canine myocardium 24 hours following ischemic preconditioning was accompanied by a significant increase in myocardial manganese superoxide dismutase (Mn-SOD) activity. These findings have been further supported by studies in vitro with rat cardiomyocytes exposed to preconditioning hypoxia.[69,87] Recent evidence suggests that the delayed protection against myocardial infarction following ischemic preconditioning,[88] or pharmacologic preconditioning with an adenosine A_1 agonist,[76] is dependent on upregulation of Mn-SOD.

The other major group of cytoprotective proteins suggested to be involved in delayed cardioprotection is the principal inducible heat shock protein, HSP70i. The involvement of this family of 'house-keeping' proteins was suggested by an early study which showed an elevation in the myocardial content of HSP70i 24 hours after ischemic preconditioning in the rabbit.[24] Further evidence in support of a role for this group of cytoprotective proteins has come from gene transfection studies[89,90] and studies with transgenic mice constitutively over-expressing human HSP70i.[91]

These findings strongly suggest a role for myocardial stress-inducible cytoprotective proteins as end-effectors of delayed preconditioning, although this is by no means proven. Indeed, evidence indicates a temporal dissociation between the expression of heat shock proteins and tolerance to ischemia,[92,93] which suggests that factors such as post-translational modification or compartmental distribution,

rather than the cellular content of heat shock proteins, might be important in inducing cardioprotection. It has been demonstrated that translocation of the small heat shock protein HSP27, and its post-translational phosphorylation may be important in mediating delayed protection against infarction in rabbits, 24 hours after transient activation of adenosine A_1 receptors.[75] A number of other gene products as yet not identified may be involved in the second window of protection and further studies are warranted in their identification and elucidation of their interaction with other mediators of this signaling cascade.

Preconditioning the human myocardium

This wealth of evidence, which indicates such a potent mode of protecting the ischemic myocardium in laboratory animals gives rise to some critical questions. Firstly, do brief episodes of ischemia also render patients resistant to subsequent sustained ischemic insult? Secondly, can the phenomenon of ischemic preconditioning be exploited to design therapeutic strategies to protect the human heart against infarction? The obvious ethical restrictions associated with studying ischemic preconditioning in man have been ingeniously circumvented in three ways: by studying surrogate endpoints of ischemia-reperfusion injury in experiments with human atrial trabeculae and ventricular myocytes; by studying patients with naturally occurring ischemic syndromes and patients undergoing planned procedures which involve brief periods of ischemia, such as coronary angioplasty (PTCA) and coronary artery bypass surgery (CABG). In the next section we will review the available evidence.

In vitro studies

Yellon and colleagues have studied human atrial trabeculae, obtained at the time of surgery, suspended in an organ bath and subjected to sustained periods of simulated ischemia.[94] It was shown that subjecting the muscle to a brief period of simulated ischemia preconditioned the tissue prior to the sustained ischemia, as evidenced by improved percentage recovery of tension during reoxygenation. It was also demonstrated that adenosine A_1 receptors may play a role in triggering this protection. More recently, involvement of PKC and K_{ATP} channels has been suggested by experiments in our laboratory using the same model of preconditioning.[52] Furthermore, early evidence suggests that mitochondrial K_{ATP} channels may be involved in mediating ischemic preconditioning in the human muscle. In this respect, selective blockade of mitochondrial K_{ATP} channels with 5-hydroxydecanoate has been shown to attenuate the protection by ischemic preconditioning in human atrial trabeculae.[95]

The role of K_{ATP} channels in this in vitro model was also demonstrated in work by Cleveland et al, who showed that atrial trabeculae obtained from diabetic patients on oral hypoglycemic sulphonylureas, which block K_{ATP} channels, could not be protected by ischemic preconditioning.[96] Furthermore, Ikonomidis et al have demonstrated preconditioning of human ventricular myocytes in cell culture using trypan blue exclusion and metabolic endpoints of injury.[97] This group have also demonstrated a role for adenosine and PKC in this model.[98] Finally, recent work by Arstall et al provides direct evidence that, in addition to classic preconditioning, human ventricular myocytes in vitro exhibit delayed cardioprotection 24 hours following a short period of simulated ischemia.[99]

Warm-up angina

Some patients are able to exercise to the point that they develop angina, rest, and then continue exercising with minimal or no further development of symptoms. This phenomenon, variably termed warm-up or first-effort angina, was for many years thought to be mediated by coronary vasodilation and recruitment of collateral vessels, which resulted in improved blood supply to the ischemic myocardium during the second period of exertion.[100]

More recent investigations, however, suggest that other mechanisms might be involved in warm-up angina. Studies examining hemodynamic and metabolic characteristics during consecutive exercise testing,[101] or consecutive angina resulting from pacing-induced tachycardia,[102] have reported a reduction in the severity of angina and the degree of ST segment depression during the second period of myocardial ischemia.

These favorable changes were not accompanied by recruitment of collateral vessels as evidenced by similar coronary and great cardiac vein blood flows measurements. However, Okazaki et al demonstrated reduced myocardial oxygen consumption during the second period of ischemia.[101] Similarly, Tzivoni and Maybaum have demonstrated a reduction in electrocardiographic evidence of silent ischemia during successive periods of exercise.[103] A study by Rinaldi et al suggested that the degree of myocardial stunning following exercise-induced myocardial ischemia may also be attenuated if the patient had performed a preceding period of exercise 30 minutes earlier.[104] Studies investigating the temporal profile of warm-up angina have demonstrated that the duration of this phenomenon is 1–2 hours following the first period of exercise, a timecourse that closely parallels that of classic ischemic preconditioning.[105,106] Moreover, it has been shown that, in addition to immediate protection, patients with stable angina have improved exercise tolerance 24 hours following a period of exercise-induced myocardial ischemia, a finding which may represent delayed preconditioning.[107]

These findings suggest that the warm-up phenomenon is at least partly due to metabolic adaptation of myocardium which induces tolerance to subsequent ischemia, a process that closely resembles ischemic preconditioning. However, studies that have examined the cellular mechanisms which mediate warm-up angina do not fully support this hypothesis. For instance, inhibition of adenosine receptors prior to exercise fails to abolish the warm-up phenomenon.[108,109] Furthermore, investigation into the role of K_{ATP} channels in mediating this form of myocardial adaptation has provided conflicting results.[110,111] It is therefore not clear at this point whether the adaptation observed during repeated exercise is a representation of the preconditioning phenomenon, or if other mechanisms are involved. Furthermore, despite attempts by some investigators, a major role for recruitment of collateral vessels contributing to this phenomenon has not been ruled out.

Preinfarction angina

Many patients experience brief episodes of ischemia before an acute myocardial infarction. It is theoretically possible that this preinfarct angina has the potential to precondition the myocardium, thereby reducing infarct size and improving survival. However, this would be the case only if the infarct-related artery is reperfused in a timely

fashion, because experimental evidence suggests that ischemic preconditioning delays necrosis and therefore has no effect on infarction in the territory of a completely occluded artery in which no reperfusion occurs. It is not surprising then that studies which evaluated the effects of preinfarct angina prior to widespread use of thrombolysis did not consistently show a beneficial effect in terms of mortality and left ventricular function.[112–114]

A number of more recent studies have evaluated the outcome of patients suffering an acute MI in relation to the presence of preinfarction angina. For example, in a retrospective analysis of the TIMI-4 trial, Kloner and colleagues showed that the presence of preinfarct angina was associated with smaller infarct size, based on peak and total creatine kinase (CK) release, improved left ventricular function with reduced incidence of congestive heart failure and shock and reduced mortality (Fig. 10.3).[115] Similar findings have been reported by other groups.[116–119] Moreover, patients who experience angina prior to acute MI seem to have reduced occurrence of life-threatening ventricular arrhythmias associated with reperfusion[116,120] and a lower in-hospital, 1- and 5-year cardiac mortality rate.[115,121,122]

Whether the protection conferred to these patients as a result of their preceding ischemic symptoms represents a form of myocardial adaptation similar to ischemic preconditioning remains a subject of debate.[123] As seen in laboratory animals, preconditioning may contribute to the improved outcome in patients with preinfarct angina, by virtue of delaying myocardial necrosis and improving post-ischemic functional recovery. Interestingly, evidence suggests that the time interval between the last episode of angina and the index MI is very important. Reports from the TIMI-9B investigators,[122] studies by Ishihara et al[121] and Yamagishi et al[124] indicate that prodromal angina is only protective if it occurs

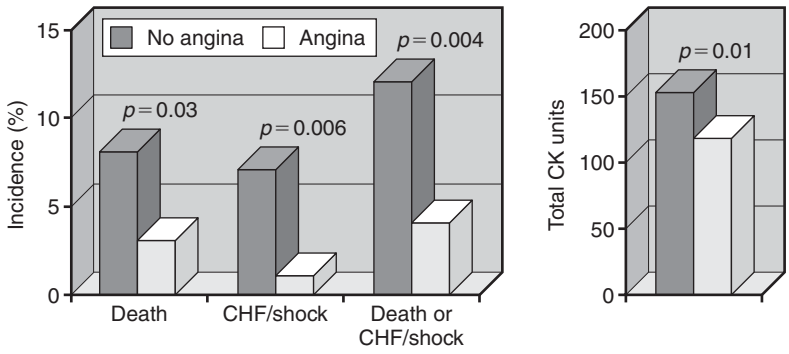

Figure 10.3
The presence of preinfarct angina induces cardioprotection. Retrospective analysis of data from the TIMI-4 trial showed a significantly improved in-hospital outcome and reduced infarct size in patients who experienced angina versus those with no preinfarct angina. CHF, congestive heart failure; CK creatine kinase. Data adapted from Kloner et al[115] with permission.

within 24–72 hours of MI; a timecourse that closely resembles that of the delayed phase of myocardial protection following ischemic preconditioning in animal models.

However, infarct size and the degree of preservation of post-ischemic left ventricular function are determined by a number of other factors in addition to the possible protection conferred by ischemic preconditioning. These factors include the extent of collateral circulation to the ischemic myocardium, time from onset of infarction to reperfusion of the infarct related artery and residual coronary stenosis after reperfusion. Studies that have analyzed the degree of collateralization to the ischemic zone after an infarction have found no increase in angiographically visible collateral vessels in patients with preinfarct angina.[115,117] It must be noted, however, that coronary angiography at 90 minutes following thrombolysis is unlikely to provide information about the degree of collateral recruitment to the ischemic zone during coronary occlusion. It is therefore difficult to rule out a contribution by collateral circulation in this setting.

In the study by Yamagishi et al, resting myocardial-dual isotope SPECT using ^{123}I-15-(*p*-iodophenyl)-3-(*R*,*S*)-methylpentadecanoic acid (^{123}I-BMIPP) and thallium (^{201}Tl) in the subacute phase of MI was employed to assess the area at risk and necrotic myocardium respectively.[124] Interestingly, these authors found that patients with preinfarct angina had significantly smaller infarcts compared to those with no preceding symptoms, in the face of no significant difference in areas of myocardium at risk. This suggests that the presence of preinfarction angina did not predict improved collateral recruitment to the ischemic zone.

Although not mutually exclusive from the mechanisms underlying ischemic preconditioning, another equally attractive hypothesis is facilitation of more rapid reperfusion of the infarct-related artery following thrombolysis in patients with preinfarct angina.[121,125] This hypothesis is based on the known inhibitory effects of adenosine, released during the brief periods of preinfarct ischemia, on platelet aggregation following activation of A_2 receptors on platelet membranes, which has been suggested to modify thrombus formation and thereby promote earlier reperfusion after thrombolysis.[126] Przyklenk and colleagues have demonstrated that, in anesthetized open-chest dogs, brief periods of ischemia prior to a long ischemic insult attenuates platelet-mediated thrombosis and improves vessel patency and that this effect is abolished by inhibition of adenosine receptors.[127,128]

Angioplasty studies

Coronary angioplasty (PTCA) provides a unique opportunity to study the response of the human myocardium to brief periods of controlled ischemia and reperfusion. The procedure usually involves repeated intracoronary balloon inflations with intervening periods of perfusion and, in theory, the first period of ischemia may enhance the myocardial tolerance to subsequent balloon inflations via classic ischemic preconditioning. In the 1990s several studies addressed this issue, using various indices of myocardial ischemia, including clinical, electrocardiographic, metabolic and hemodynamic measurements. Most, but not all,[129] have shown that if the duration of the first inflation is longer than a 'threshold' of approximately 60–90 seconds all indicators of myocardial ischemia, including chest pain severity, abnormalities of left ventricular regional wall motion, ST segment elevation,

QT dispersion, ventricular ectopic activity, lactate production and release of myocardial markers such as CKMB are attenuated during subsequent balloon inflations, providing evidence for myocardial adaptation induced by the first period of ischemia.[130–134]

As with many studies of ischemic preconditioning in man, a major confounding factor during successive balloon inflations in PTCA studies is the acute recruitment of collateral vessels. However, studies that have been controlled for this effect by angiographic grading of the collateral vessels,[131] measurement of cardiac vein flow,[130] changes in blood flow velocity in the contralateral coronary artery[135] and more accurately, by assessment of intracoronary pressure derived-collateral flow index during successive balloon inflations,[136] have shown that collateral recruitment occurs in some patients, it cannot fully explain the myocardial adaptation observed during repeated balloon inflations.

Investigation into the mechanisms underlying this rapid protection of the myocardium during PTCA has provided further support for a preconditioning-like effect. Tomai et al reported that blockade of K_{ATP} channels with oral glibenclamide prior to angioplasty abolishes the reduction in ischemic indices observed during subsequent balloon inflations, implying a role for these channels in mediating this form of adaptation.[137] This finding is supported by the observation that opening of these channels with niorandil reduces the electrocardiographic indices of ischemia during PTCA.[138]

Furthermore, an important role has been demonstrated for adenosine in mediating myocardial adaptation during coronary angioplasty. Inhibition of adenosine receptors by bamiphylline[108] or aminophylline[139] abolishes myocardial adaptation during the second balloon inflation. Independent of its vasodilatory effect, intracoronary infusion of adenosine prior to PTCA conversely attenuates ischemic indices during the first balloon inflation (Fig. 10.4).[140] Reports have also suggested a role for both opioid[141] and bradykinin[142] receptors in mediating myocardial adaptation during PTCA. These studies provide further evidence that myocardial tolerance to further ischemic episodes can be induced by preceding brief periods of ischemia, and that this tolerance may be mediated by the same mechanisms as those involved in ischemic preconditioning in animal models.

Experimental evidence has also provided grounds for caution when interpreting the results of these PTCA studies. Many studies used ST segment elevation on the surface or intracoronary ECG as an endpoint which reflects the degree of myocardial ischemia and its attenuation during successive balloon inflations as an indicator of enhanced myocardial resistance to ischemia. Although this assumption was supported by earlier experimental studies of repeated coronary artery occlusion in collateral-deficient pig and rabbit hearts,[143,144] a recent study by Downey and colleagues clearly indicates a dissociation between ST segment changes on the electrocardiogram and myocardial protection in terms of infarct limitation.[145] They found that the changes in ST segment voltage during coronary artery occlusion may merely represent an epiphenomenon distinct from the cardioprotective effect of ischemic preconditioning. This finding is particularly pertinent when evaluating or designing mechanistic studies using pharmacologic agents to mimic or to abolish the cellular signaling mechanisms of ischemic preconditioning. It is imperative

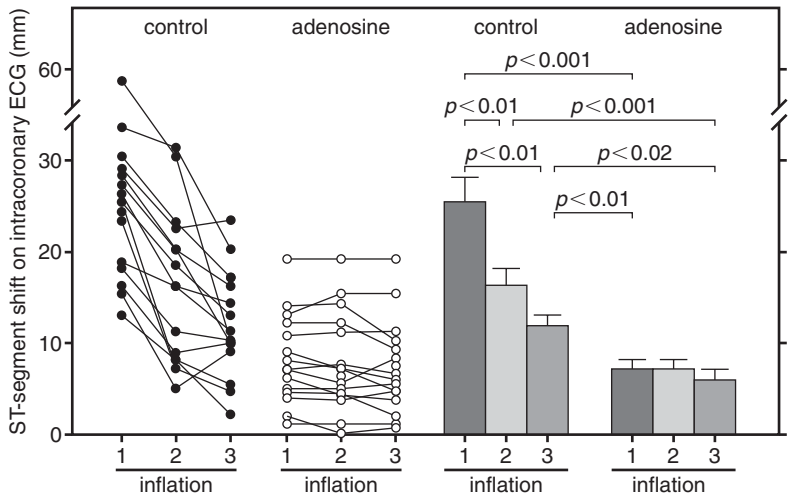

Figure 10.4
Myocardial adaptation with successive balloon inflations during coronary angioplasty. Individual (left) and average (right) values of ST-segment shift on the intracoronary ECG at the end of the first, second, and third balloon inflations in control patients, and those treated with an intracoronary infusion of adenosine. In control patients, there is a progressive reduction in ST-segment elevation from the first to the third balloon inflation. In adenosine-treated patients, the ST-segment shifts are similar between the different inflations and are less than that seen in control patients. Reproduced from Leesar et al[140] with permission.

that the influence of these pharmacologic tools on the sarcolemmal K_{ATP} channels, thought to modulate ECG voltages, is clearly distinguished from their effect on the mitochondrial K_{ATP} channels which have been proposed as a mediator of cardioprotection.[146]

CABG studies

Possibly the most direct evidence for preconditioning in man comes from studies that have examined whether a specified preconditioning protocol can protect the human myocardium from the period of global ischemia induced by aortic crossclamping during coronary artery bypass grafting (CABG). Yellon et al reported a prospective study to examine the effects of a preconditioning protocol of two cycles of 3 minutes of global ischemia (induced by intermittent cross-clamping the aorta and pacing the heart at 90 beats/min) followed by 2 minutes of reperfusion prior to a 10-minute period of global ischemia and ventricular fibrillation.[147] The changes in ATP content in needle biopsies of left ventricular muscle were used as the endpoint in this study. Patients subjected to this preconditioning protocol had better preservation of ATP levels during the subsequent global ischemic period.

These findings were almost identical to those observed in canine hearts by Murry et al.[148] The preconditioned dogs that showed this relative preservation of ATP during the early stages of prolonged ischemia sustained significantly smaller infarcts at the end of a 40-minute period of ischemia. Myocardial necrosis was not estimated in the original human study. In a more recent study by Yellon et al, serum levels of Troponin-T were used as an indicator of myocardial cell necrosis in the same model.[149] Using this endpoint, patients subjected to the preconditioning protocol suffered significantly less myocardial necrosis during the 10-minute period of global ischemia. In another recent study, a preconditioning protocol of 1 minute of aortic cross-clamping followed by 5 minutes of reperfusion immediately before cardioplegic arrest, resulted in a significant improvement in post-operative cardiac index and reduced requirement for inotropic support compared to the non-preconditioned group.[150]

Studies that have used other cardioprotective strategies during the prolonged period of ischemia, such as hypothermia or cardioplegia, have not consistently demonstrated additional protection by ischemic preconditioning. For instance, Perrault and colleagues used a similar preconditioning protocol of one 3-minute episode of aortic cross clamping before the onset of cardioplegic arrest.[151] This study failed to show any beneficial effects compared to the control group, in fact the preconditioned group of patients had more CK release compared to case-matched controls. Similarly negative results have been reported by another group.[152] These divergent results have led to the hypothesis that, in the CABG setting, the additional protection conferred by ischemic preconditioning may only be demonstrable where a potential for suboptimal myocardial protection increases the risk of perioperative infarction.[153] However, this hypothesis is not supported by recent studies that indicate improved myocardial preservation by ischemic preconditioning during CABG or valve surgery despite optimal protection with hypothermia and cardioplegia.[150,154] Resolution of these discrepancies is obviously required before brief antecedent ischemia can be advocated as a means of prophylactic therapy.

Therapeutic implications

It can be deduced from the evidence outlined above that the human myocardium is amenable to preconditioning and also that preconditioning occurs as a natural feature of some ischemic syndromes. Two important questions arise regarding the applicability of ischemic preconditioning that need careful consideration. First, are there areas in clinical medicine in which therapeutic preconditioning may benefit patients with ischemic heart disease? Second, can the naturally occurring preconditioning that follows ischemic syndromes (such as angina) be exploited, and does treatment of the symptoms abolish any possible cardioprotective effects?

Pharmacologic preconditioning

Early revascularization strategies remain the most effective means of limiting ischemic injury. The time interval between the onset of symptoms and initiation of revascularization is however crucial, and the benefits of treatment diminish as this interval increases.[155] Preconditioning, by virtue of delaying myocardial necrosis, prolongs the time window during which

revascularization therapies can be administered. Although the use of brief antecedent ischemia as a prophylactic measure is not desirable or feasible in most circumstances, the use of pharmacological agents that mimic the protective effects of preconditioning may provide a more benign approach. Potential candidates currently in clinical use include adenosine, or its analogs, and K_{ATP} channel openers, such as nicorandil. Such strategies however, would require pretreatment – the myocardium must be preconditioned prior to the onset of ischemia. There are certain situations in which the timing of treatment before the onset of ischemia can be controlled to an extent.

The acute coronary syndromes (ACS) comprise a spectrum of pathophysiologic conditions that span unstable angina, non-ST-elevation MI and acute ST-elevation MI. In patients with acute MI with persistent ST-elevation, early reperfusion to re-establish epicardial blood flow is well established as the standard of care, either with early fibrinolytic therapy or primary angioplasty.[156] As far as pharmacologic preconditioning strategies are concerned, these patients are unlikely to benefit from such treatment, and their management should focus on early restoration of coronary artery patency and potential strategies to minimise reperfusion injury.

Non-ST-elevation ACS, including unstable angina and non-Q-wave MI, mark the transition from stable coronary artery disease to an unstable state, and constitute the leading cause of hospital admission in patients with coronary artery disease. This group of patients are at a high risk of progression to acute coronary occlusion, and more than 10% die or suffer an MI (or reinfarction) within 6 months, with about one half of these events occurring during the acute early phase.[157]

This cohort of patients with non ST-elevation ACS, form a reasonably well defined high risk group who might benefit from pretreatment with agents that trigger or augment myocardial preconditioning over a period of several days or weeks and could therefore effectively maintain the myocardium in a protected or 'preconditioned' state. A number of these patients who suffer a myocardial infarction following their unstable symptoms may be 'naturally' preconditioned by their preceding ischemic episodes. Evidence suggests, however, that this natural protection is limited to those patients in whom the episodes of preinfarct angina occur during a narrow time window in relation to the infarct.[121,122]

Even when prior treatment with the pharmacologic preconditioning agent is feasible, the duration of the protection afforded is limited. The temporal profile of the protective effects of preconditioning in man is unknown but, according to experimental evidence in laboratory animals, is unlikely to exceed 48–72 hours.[26,71] Therefore, unless the onset of an ischemic event can be predicted with accuracy, repeated dosing with the potential preconditioning drug will be necessary in these high-risk patients in order to maintain the preconditioned state. Early experimental evidence suggested that the protective effects of 'classic' ischemic preconditioning are lost after prolonged periods of repetitive ischemia,[23] or chronic pharmacologic preconditioning with selective adenosine A_1 agonists.[158] However, encouraging evidence indicates that tachyphylaxis could be overcome by exploiting the prolonged timecourse of the 'second window of protection'. Intermittent treatment of conscious rabbits with an optimal dosing regimen of pharmacologic preconditioning with selective adenosine A_1 receptor agonists maintains

the animals in a preconditioned state over a period of several days and results in a significant reduction in infarct size.[74,159]

Very few studies have evaluated a protective role for pharmacologic preconditioning strategies in patients with non-ST-elevation ACS. A report by Patel et al[160] suggests that opening of K_{ATP} channels with nicorandil, in addition to standard aggressive medical therapy for unstable angina, results in a significant reduction in the incidence of myocardial ischemic episodes and tachyarrhythmias. This may purely represent an anti-ischemic effect due to the vasodilatory properties of nicorandil. However, since the patients in this study were already on maximal antianginal therapy, and in particular a significant proportion were treated with intravenous or oral nitrates, it is possible that the protection observed in the nicorandil group, be it only using soft endpoints of myocardial injury, may be due at least partially to a preconditioning-like effect.[161] These encouraging findings, coupled with more recent experimental evidence which indicates that nicorandil specifically activates the mitochondrial rather than the sarcolemmal K_{ATP} channels in rabbit ventricular myocytes,[162] provide a promising new approach to myocardial protection in patients with unstable angina.

Preconditioning strategies might also be applied prior to planned procedures that involve a potentially injurious ischemic insult, such as CABG or PTCA. Highly effective methods of myocardial protection during coronary artery surgery have been developed, including chemical cardioplegia, hypothermia and cross-clamp ventricular fibrillation. However, with increasing number of operations on older and higher risk patients, there is always a need for improved protection.

Therapies that stimulate preconditioning mechanisms, administered prior to such operations have the potential to provide this increased protection. For instance, adenosine, an important mediator of the preconditioning phenomenon in human atrial trabeculae[94] and during PTCA,[140] has been shown to result in improved post-operative left ventricular function when used as an additive to blood cardioplegia[163] or administered intravenously prior to cardiopulmonary bypass.[164]

Similarly, although routine PTCA carries a small risk (<5%) of complete coronary occlusion and MI, high risk patients undergoing PTCA might benefit from pretreatment with agents that mimic preconditioning or augment the protection afforded by the first balloon inflation. A study by Heidland et al has demonstrated that an intracoronary infusion with the adenosine agonist dipyridamole prior to PTCA resulted in enhanced tolerance to prolonged balloon inflations and a significant reduction in post-procedural left ventricular dysfunction.[165] The possibility that organ preservation prior to transplantation might be amenable to the same improved protection, as suggested by some experimental evidence,[166–168] is also of significant interest. This might allow an extension of the 'cold ischemic time' between harvesting and implantation, facilitating optimal matching of recipient to donor, as well as affording a potential improvement in early myocardial function.

'Natural' preconditioning

In considering whether angina induces preconditioning and if treating the symptoms of angina abolish this protection, the evidence must be viewed with caution. It must be emphasized that extension of the evidence

reviewed above in favour of preconditioning to routine clinical practice is speculative at this stage. However, considering the current evidence for the mechanisms that underlie myocardial adaptation, we can question the choice of drug treatment for patients with angina. For example, the probable involvement of K_{ATP} channels, as the effector protein mediating the cardioprotective effects of preconditioning, favours the use of the K_{ATP} channel openers such as nicorandil.

Conversely, the increased mortality from ischemic heart disease observed in diabetic patients on oral hypoglycemic therapy, begs a radical review of drug treatment of diabetic patients with angina,[169] since sulphonylureas, the most widely used oral hypoglycemic agents, block K_{ATP} channels and the possible cardioprotective effects of ischemic preconditioning. Similarly, the demonstration that antagonism of adenosine receptors prevents ischemic preconditioning during PTCA[135,139] and in human atrial trabeculae,[94] questions the use of agents such as methylxanthines in high-risk patients such as those with unstable angina or those undergoing revascularization procedures.

Conclusion

A wealth of evidence supports the concept that ischemic preconditioning profoundly and consistently limits infarct size in the experimental laboratory. Several lines of evidence obtained from human myocardial tissue, from the catheterization laboratory and the operating theatre, and from analyses of large clinical trials suggest that the human myocardium may behave in a similar way. There are several classes of pharmacologic agents that may be able to mimic the protection conferred by ischemic preconditioning and provide some basis for optimism that a beneficial and clinically detectable improvement in myocardial protection may be possible.

In the short term, further studies in routine (low-risk) patients must be performed to establish the safety of these agents, with multiple endpoints to detect small differences in myocardial viability and extent of micronecrosis. In the longer term, however, large scale studies involving high-risk patients are warranted to investigate the potential cardioprotective effects of these agents, with comparisons against pre-existing myocardial protective strategies. With a more complete understanding of the mechanisms underlying myocardial adaptation, we can look forward to development of new therapeutic agents with novel mechanisms of action to supplement current treatment options for patients with ischemic heart disease.

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11

The Role of ACE Inhibitors in Coronary Artery Disease

Michael Schachter

Introduction

The angiotensin converting enzyme (ACE) inhibitors have made a spectacular impact on cardiovascular therapeutics, almost certainly beyond the expectations of those who developed them. The ACE inhibitors are widely used in hypertension generally and even more in diabetic hypertensives. They have also assumed a crucial role in the treatment of heart failure and in secondary prevention following myocardial infarction (MI). It has recently been suggested that virtually all patients with atherosclerosis are potential candidates for ACE inhibitors, in the absence of contra-indications and intolerance.[1] Although of course hypertension and coronary artery disease commonly co-exist, this chapter will not deal with ACE inhibitors as antihypertensive drugs but will focus on the basic mechanisms and the practicalities of their other uses. Ideas in this area have changed greatly since 1990, as it has become clear that angiotensin II has a much wider range of cardiovascular effects than had been supposed.

Basic mechanisms

The 'classical' view of the renin-angiotensin-aldosterone (RAS) system envisages it as a humoral system (Fig. 11.1). It produces angiotensin II, a potent vasoconstrictor, and aldosterone, which inhibits sodium excretion. It is therefore rational to consider the RAS as a system which increases peripheral resistance and expands extracellular and circulating volume: in hemodynamic terms, it increases afterload and preload. Although there is no reason to doubt that this view is relevant, there are now reasons to take a wider perspective:

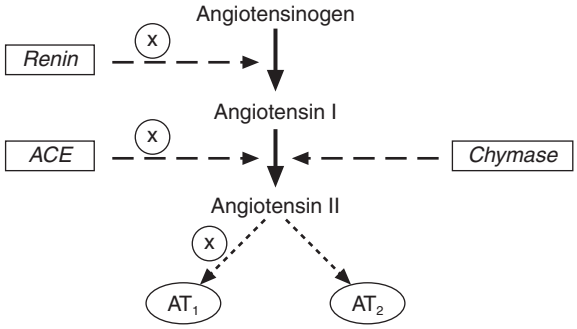

Figure 11.1
The renin-angiotensin system, showing sites (marked with x) where pharmacologic intervention is possible. Clinically usable renin inhibitors are not available at present. Stimulation of aldosterone synthesis, and the actions listed in Table 11.1, are all mediated via AT_1 receptors.

Growth factor for vascular smooth muscle
Chemotactic factor for vascular smooth muscle
Increased oxidative stress (via superoxide generation)
Impaired endothelial function
Increased expression of inflammatory mediators and adhesion molecules
Decreased fibrinolysis/increased thrombogenesis
Activation of monocytes/macrophages
Increased blood pressure

Table 11.1
Actions of angiotensin II which may promote atherogenesis and coronary artery disease.

- It is clear that angiotensin II has importance as a local mediator, which is synthesized in many tissues, including the heart and the vascular wall.[2–4]
- The cardiovascular effects of angiotensin II are now known to extend far beyond vasoconstriction (Table 11.1),[5] a list which continues to expand. Its extent is perhaps not so surprising if the RAS is regarded as a stress-response mechanism similar to the sympathetic nervous system. The two have of course important interactions.

Some of the cardiovascular effects of angiotensin II will now be discussed in greater detail.

Antiatherogenic effects

There is experimental evidence that ACE inhibitors do inhibit atherogenesis in several animal models,[6,7] presumably in part through their effect on the processes listed in Table 11.1. Angiotensin II is a growth factor, though of variable efficacy, for vascular smooth muscle cells.[8,9] As such it may promote the growth of atheromatous plaques, as part of the response to injury. Its chemotactic effect in promoting smooth muscle cell migration may also contribute to atherogenesis.[10] In both cases its importance may be as a co-factor with more potent proteins, such as platelet-derived growth factor. As always it is difficult to establish how relevant these data might be in the context of human vascular disease, but it is reasonable to presume that the diminished concentration or activity of angiotensin II will be beneficial.

Angiotensin II is also a potent *activator* of *oxidative stress* in vascular cells, leading to increased generation of oxygen free radicals, with the superoxide anion as the primary product.[11] The principal enzyme involved is analogous to the oxidase responsible for the oxidative burst in phagocytic cells, although it is much less active. The free radicals may act as intracellular messengers for the growth-promoting action of angiotensin II, but this is less well established than the fact that they destroy nitric oxide, normally produced by the endothelium.[12] Nitric oxide counteracts all the effects attributed to angiotensin II in Table 11.1.[5,13] It is also interesting that raised levels of plasma cholesterol contribute to oxidative stress and in addition cause up-regulation of the AT_1 receptor sub-type, which mediates most of the cardiovascular effects of angiotensin II.[14,15] Furthermore, the peptide is now also seen as a promoter of inflammation, a crucial component of the atherosclerotic process.[16,17] This is partly mediated through free radical generation but also through the expression of specific cytokines.[18]

Endothelial function

It is likely that the effects of the ACE inhibitors on endothelial function are central to their antiatherogenic effects.[19] Direct clinical evidence of such an effect is lacking but large-scale studies are currently in progress. It is not only through reduced angiotensin II generation that ACE inhibitors can favourably influence endothelial function. As Fig. 11.2 indicates, these drugs also inhibit the kininase responsible for the breakdown of bradykinin (and also of substance P). Bradykinin in particular is known to act directly on endothelial cells to increase nitric oxide release. The relative importance of these two actions of the ACE inhibitors has become increasingly controversial since the introduction of angiotensin receptor (AT_1) antagonists (see later).

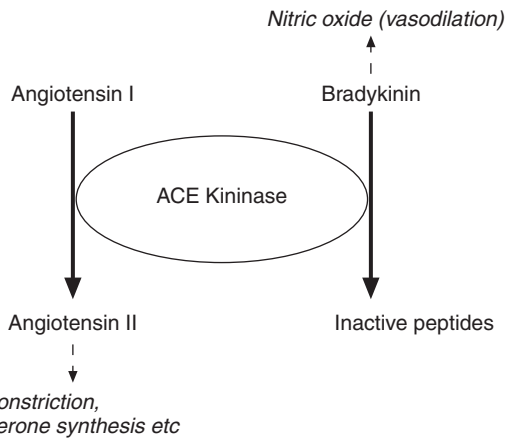

Figure 11.2
Actions of angiotensin converting enzyme/kininase and some functional implications. Part of the effect of bradykinin on the endothelium is direct and part is mediated through increased prostaglandin synthesis.

The TREND study was the first to demonstrate directly that ACE inhibitors improve coronary endothelial function in normotensive patients with atheromatous plaques.[20] Many other trials are in progress dealing with this issue, if not always as a primary objective or endpoint. In the last few years there has been increasing focus on stabilization of the atheromatous plaque as a therapeutic goal in the prevention of coronary events and one can suppose that ACE inhibitors will contribute to this, often in conjunction with lipid-lowering therapies

Myocardial protection

At one time this heading would have suggested primarily the prevention or reversal of left ventricular (LV) hypertrophy in hypertension. This is undoubtedly important but it is now clear that the ACE inhibitors also have significant benefits in other circumstances, notably following MI and in patients with heart failure. The ACE inhibitors diminish ventricular remodelling, which may occur relatively quickly after infarction and more gradually in heart failure of whatever etiology.[21,22] Exactly how this is achieved is not clear. Certainly some of the benefit is hemodynamic and related to reduced LV end-diastolic pressure, that reduces wall stretch and tension. However, other mechanisms may also be important: specifically reduced synthesis of collagen and reduced levels of myocyte apoptosis.[23,24] These effects are thought to be mediated by reductions in aldosterone and angiotensin II levels.[25] Once again, the relative importance of bradykinin remains controversial, but the overall result is greater preservation of viable myocytes, less fibrosis and smaller ventricular end-diastolic volume.[25]

Angina

It is not surprising that several studies have examined the possible use of ACE inhibitors in angina. One might expect a beneficial effect as a result of improved LV and endothelial function. In fact, results have been uniformly disappointing, with at best a very modest response and generally no response at all.[26,27] An interesting ancillary effect of the drugs has emerged, however, in patients treated with long-acting nitrates. Concomitant treatment with ACE inhibitors retards the development of nitrate tolerance, apparently maintaining the cyclic GMP response to nitrates in vascular smooth muscle.[28,29] The mechanism is not known.

Management

The remainder of this chapter will summarize and discuss the clinical applications of the ACE inhibitors in patients with coronary artery disease, under two main headings:

- Congestive heart failure and its prevention
- Secondary prevention post-myocardial infarction

Congestive heart failure

The ACE inhibitors are widely regarded as having two closely related roles in the patient with heart failure: the treatment of established heart failure and the prevention of disease progression. ACE inhibitors were the first drugs shown to have a significant impact on mortality from all grades of heart failure, although spironolactone and beta blockers have now been shown to improve outcomes in mild to moderate heart failure.[30,31] The rationale for the use of ACE inhibitors in these patients is well-recognized (Table 11.2) and their efficacy has been demonstrated in several large clinical trials. These are summarized below.

Reduced preload
Reduced afterload
Reduced sodium/water retention direct renal vascular/tubular effect reduced aldosterone secretion
Reduced cardiac remodelling/fibrosis
?Improved coronary reserve

Table 11.2
Rationale for the use of ACE inhibitors in heart failure.

CONSENSUS

The CONSENSUS I study[32] was the first to demonstrate the efficacy of ACE inhibitors. It included 253 patients with severe heart failure (New York Heart Association (NYHA) class IV), randomized to placebo or enalapril 2.5–40 mg daily. The patients had a mean age of 70 years, and 70% were male. The follow-up period ranged from 1 day to 20 months, with an average of just over 6 months. The reduction in mortality in the enalapril group, compared to placebo, was 40% at 6 months and 31% at 1 year. The absolute risk reduction was approximately 18% at 6 months. There was also a reduction in NYHA class and in heart size.

SOLVD (T)

The SOLVD (T) trial[33] was very much larger, involving over 2,500 patients randomized to placebo or enalapril. The patients all had overt

heart failure, with mean ejection fractions of 0.25, but over half were in NYHA class II and only 2% were in class IV. The patients were also younger, with a mean age of about 61 years. The mean follow-up period was about 3.5 years and enalapril dosage ranged from 5–20 mg daily. The relative risk reduction, for mortality, was only 16.0%, with 4.5% reduction in absolute risk. There was some improvement in quality of life in the treated patients but this was relatively modest. The even larger SOLVD (P) prevention trial will be discussed in the context of post-myocardial infarction studies (see p. 6).

VHeFT II

VHeFT II[34] compared enalapril not against placebo but against a combination of hydrallazine and isosorbide dinitrate. VHeFT I had shown that vasodilators (hydrallazine or prazosin combined with the nitrate) reduced mortality by 25% over 2 years. Over 800 male patients were enrolled in VHeFT II, approximately 50% classified as NYHA II and III and a very small minority in class IV. Mean follow-up was 2.5 years with an enalapril dose of 20 mg per day. At 2 years, mortality was 25% in the vasodilator group compared to 18% in the enalapril group. Most of the difference was due to reduced occurrence of sudden death in the ACE inhibitor group. Interestingly, there was greater improvement in ejection fraction in the other treatment group.

Following MI

This has proved a slightly more contentious topic, partly at least reflecting the heterogeneity of the clinical trials. The main issue here has been the distinction between:

- Trials which included virtually all post-MI patients, and
- Trials which selected patients at particularly high risk.

These will be summarized separately.

Non-selective trials

CONSENSUS II

The Scandinavian CONSENSUS II trial[35] investigated the effect on mortality of the early treatment with an ACE inhibitor (enalapril) post-MI. Over 6000 patients were randomized to treatment or placebo and followed-up for 6 months. Enalapril dosage ranged from 5–20 mg/day and treatment started within 24 hours of the infarct. The study was terminated early because there was clearly no improvement in outcome in the treated group.

GISSI-3

The Italian GISSI-3 study[36] was even larger, with nearly 19 000 patients randomized, but also more complex in design. It sought to examine the effects on outcome of an ACE inhibitor, lisinopril, and of glyceryl trinitrate, separately and in combination. Again, treatment began very soon post-MI and continued for up to 6 weeks, with lisinopril dosage between 5–10 mg/day. At 6 months, 18.1% of patients on lisinopril had died or developed severe LV dysfunction, compared to 19.2% of those on placebo. Given the large numbers in the study, this is statistically significant but clearly represents a very modest benefit. Analysis of the data in fact showed that almost all of the benefit was confined to patients with initial LV dysfunction.

ISIS-4

The multinational ISIS-4 study[37] was larger still (over 58 000 patients) and even more

complex. It attempted to define the benefit, if any, of early intervention with the ACE inhibitor captopril, isosorbide mononitrate and intravenous magnesium. Captopril was started within 24 hours with a test dose of 6.25 mg and titrated up to a maximum of 100 mg daily. The principal assessment was at 5 weeks, although patients were followed for 6–12 months. The benefit was again statistically significant but modest: the event rate at 5 weeks was 7.7% in the placebo group as compared to 7.2% in the captopril group, a relative risk reduction of about 7%. The benefit was once again much greater in the high risk patient (evidence of LV dysfunction, anterior, or anterior plus inferior MI, and history of previous MI).

SOLVD (P)

It may be appropriate to discuss the SOLVD (P) trial[38] under this heading, although it does not fit precisely into any category. Over 80% of the 4228 patients recruited were survivors of MI, but not within the previous 30 days. As in the 'treatment' arm of the trial, SOLVD (T), patients had poor LV function with ejection fractions below 0.35. The treatment design was similar in the two trials. In SOLVD (P) there was an 8%, statistically non-significant reduction in total mortality, but with a highly significant reduction of 29% in the combined endpoint of death and the development of congestive heart failure.

Selective trials

These trials are broadly contemporary with the non-selective trials described above, rather than prompted by them. Obviously the selective trials differ in attempting to identify patients most likely to benefit from treatment with ACE inhibitors, but they also diverge in two other significant respects: all but one initiate treatment later than 24 hours post-MI; and follow-up periods are years rather than weeks or months. The major studies are summarized below.

SAVE

The SAVE trial[39] included over 2200 post-MI patients with ejection fraction $\leq$40%, as assessed by radionuclide ventriculography, but without overt heart failure. Captopril, or placebo, was started 3–16 days after the infarct, with a test dose of 6.25 mg followed by titration to a maximum of 150 mg daily. Mean follow-up was 3.5 years and up to 5 years in some patients. The reduction in mortality was 19% ($p = 0.019$), and there was also significantly reduced risk of recurrent MI or coronary revascularization.

AIRE

In the AIRE study[40] patients were recruited with overt cardiac failure post-MI. There were 2006 patients who had proven MI 3–10 days before randomization and were treated with ramipril 5–10 mg daily, or placebo. Follow up ranged from 6–30 months with a mean of 15 months. There was a highly significant reduction in mortality of 27% ($p = 0.002$), with clear benefit evident within a month.

Three years after the formal end of this trial, all 600 patients from British centres were identified and it was found that 39.0% of placebo-treated and 27.5% of ramipril-treated patients had died, a relative risk-reduction of 36% (AIREX).[41]

SMILE

The SMILE trial[42] identified high-risk individuals by a different approach. The patient population of over 1500 consisted of those

who had suffered an anterior MI but who had not received thrombolysis, in other words, patients at a high risk of severe myocardial damage. Treatment was started within 24 hours with zofenopril (15–60 mg daily after titration) or placebo, with overt heart failure as a specific exclusion criterion. Treatment was continued for 6 weeks and patients were assessed at that time and also at 1 year. After 6 weeks there was a reduction in mortality of 34% in the patients treated with ACE inhibitor. After 1 year, the reduction was still 29%. At the earlier time point, there was a 46% reduction in risk of severe heart failure.

TRACE

Patients in the TRACE study[43] were recruited 3–7 days post-MI on the basis of an ejection fraction ≤35% measured by echocardiography. A total of 1749 patients were assigned to treatment with trandolapril or placebo. After a test dose of 0.5 mg, trandolapril dosage was increased by up to 4 mg daily during a follow-up period of 24–50 months. Mortality was reduced by 22% (the risk of sudden death was diminished by 24%) and there was 29% reduction in the risk of progression to severe heart failure.

FAMIS

The FAMIS trial[44] was restricted to patients with definite anterior infarction who had been treated with early thrombolysis. These patients were thus at higher risk because of the site of the infarct, but with benefit from early intervention. The population was relatively modest (285) and was randomized to fosinopril 5–20 mg daily, started within 9 hours of the onset of symptoms. Treatment was continued for 3 months but follow-up continued for an average of 2 years. At this time point, there was no difference in mortality between placebo and fosinopril-treated patients but there was a 30% reduction in the combined endpoint of death or moderate-severe heart failure. This included patients who had heart failure on admission.

After revascularization

Two studies have investigated the value of ACE inhibitors after revascularization. The QUO VADIS trial[45] enrolled nearly 150 patients undergoing elective coronary bypass graft surgery, who received quinapril 40 mg daily or placebo for a year. All had normal blood pressure and LV function. There was an 80% reduction in ischemic events, which occurred in 18% of the patients in the placebo group. Blood pressure levels were similar in the two groups. In the APRES study[46] 159 patients were recruited following bypass grafting or angioplasty and treated with ramipril or placebo with a median follow-up period of 33 months. Patients had ejection fractions between 0.30 and 0.50 but did not have overt heart failure. The composite end-point included cardiac death, acute MI and clinical heart failure and was reduced by 58% ($p = 0.031$) in the ramipril-treated group.

The HOPE study

The HOPE study[47] has already had a major impact on clinical thinking about ACE inhibitors, and has been the prime motive force in encouraging physicians to consider their more extensive use. The effect of the ACE inhibitor ramipril was assessed in over 9000 patients who either had definite atherosclerotic cardiovascular disease (80% had coronary artery disease, 43% had peripheral

vascular disease and 11% had suffered as stroke or transient ischemic attack) or were diabetic with at least one other risk factor. In fact 38% of the patients were diabetic. Nearly half the patients were hypertensive but they were treated with antihypertensive drugs other than ACE inhibitors before entering the trial. Patients with congestive heart failure or significantly impaired LV function were excluded. Patients were randomly allocated to placebo or ramipril 10 mg daily. The primary endpoint was a composite one, including MI, stroke and death from cardiovascular disease.

The trial was stopped prematurely, before 5 years, because of a clear advantage in the treated group of patients, who showed a 22% reduction in the primary endpoint ($p < 0.001$). There were comparable reductions in the component endpoints and, unexpectedly, a one-third reduction in the number of new diabetic patients. Benefits of treatment were clear in all sub-groups, including those with pre-existing diabetes. The blood pressure reduction, of 3/2 mmHg, was considered too small to account for the observed benefit. On the basis of these findings it has been estimated that treatment with ramipril prevented nearly 130 events per 1000 patients over 4–5 years in about 60 patients. This analysis is on an intention-to-treat basis and may therefore underestimate actual benefit. The implications of the study for clinical practice are still not finally determined, although among the HOPE investigators there is certainly support for the much more widespread use of ACE inhibitors.[48] Importantly, this study reinforces the case for the use of ACE inhibitors in diabetic patients who are not hypertensive.[49]

Current trials

Despite the volume of data and the advent of the angiotensin II receptor blockers (see below), several medium- to large-scale clinical trials are in progress with the ACE inhibitors in several areas of cardiovascular disease. The principal studies are summarized below:

- *SECURE* (~700 patients, 4 years):[50] is a sub-study of HOPE, where the effect of the treatments on carotid atherosclerosis is documented using B-mode ultrasound.
- *PEACE* (>8000 patients, 5 years):[51] is also intended to test the hypothesis that an ACE inhibitor (in this case trandolapril) will reduce the incidence of cardiovascular events in patients with known coronary artery disease.
- *QUIET* (1750 patients, 3 years):[52] designed to determine whether quinapril can reduce the rate of progression of atherosclerosis in patients who had undergone coronary angioplasty or atherectomy. The angiographic sub-study failed to show an effect on the rate of restenosis.[53]
- *EUROPA* (>10 000 patients, ≥3 years):[54] will study the effect on cardiovascular endpoints in a population of patients with documented coronary artery disease treated with perindopril or placebo.

Which ACE inhibitor, at what dose?

Differences between ACE inhibitors

Are all ACE inhibitors equal? In several respects they are not:

- ACE inhibitors have widely differing pharmacokinetic profiles,[55] more readily reflected in antihypertensive therapy than in the treatment of heart failure.[56] It must be presumed that suppression of angiotensin II levels is a prerequisite for the efficacy of ACE inhibition. This can be achieved by single daily doses of long-acting agents (e.g. perindopril, trandolapril) or by twice-daily doses of shorter-acting ones (e.g. enalapril, ramipril). Since heart failure is, regrettably, a symptomatic condition in contrast to hypertension, once-daily dosing may be less critical for compliance. However, the dose itself *must* be adequate (see below).
- ACE inhibitors have differing affinity for tissue ACE as opposed to circulating or endothelial ACE. A distinction can be made between ACE inhibitors that have affinity for the tissue-bound enzyme (such as quinapril) and those that do not (including enalapril).[57] Recently it has been proposed that this is relevant to the different effects of these drugs in the peripheral circulation of patients with heart failure. Quinapril, or rather the active form quinaprilat, increased flow-dependent vasodilation while enalaprilat did not.[58] The nitric oxide-dependent component was particularly enhanced, and this was interpreted as a consequence of tissue bradykinin accumulation. Although this difference in enzyme may also be relevant in other tissues, notably the heart, its clinical importance is at present wholly unknown.
- There may be differences in adverse effects between ACE inhibitors. Captopril is the longest-established of the ACE inhibitors and was initially used at what would now appear to be very high doses (450 mg daily, or even higher). At that time it appeared to have a very high incidence of adverse effects, such as taste disturbance, rash, bone marrow dyscrasia and nephrotic syndrome. These were attributed, probably rightly in part, to the sulphydryl moiety of captopril, which was lacking in other ACE inhibitors. However, reduction in dosage to $\leq$150 mg daily drastically reduced the incidence of these problems to levels comparable to other, later, ACE inhibitors. The most troublesome side-effects of these drugs – reduced kidney perfusion in renovascular disease, angioedema and dry cough – are class- not drug-dependent.

Overall therefore, there is at present no firm basis for preferring any particular ACE inhibitor provided each is used at equivalent doses and appropriate dosage intervals.

The importance of dose

It may seem too obvious to state, but the dosage of therapeutic agents does, of course, matter. The multinational ATLAS trial (not yet published in full)[59] showed that patients with heart failure treated with relatively high doses of lisinopril (30 mg daily) had a trend towards improved survival compared to those taking 5 mg daily or even less. Rates of hospitalization were significantly reduced, while the incidence of side-effects was not greater in the high-dose patients. In fact, more patients withdrew from the low-dose group.

Angiotensin II receptor antagonists vs ACE inhibitors

In terms of cellular and molecular mechanisms, much is already known about how angiotensin II receptor antagonists compare

Most potentially harmful effects of angiotensin II are mediated via AT_1 receptors
ACE inhibitors may not fully inhibit angiotensin II synthesis
Failure of ACE inhibition can occur after initial success
Many side-effects of ACE inhibitors are due to accumulation of peptides, such as bradykinin

Table 11.3
Rationale for the possible use of angiotensin AT_1 blockers.

with ACE inhibitors. With respect to clinical data, other than in hypertension, much less has been established.[60] Why think about alternatives, or even replacements, for such a strikingly successful class of compounds? Table 11.3 suggests some reasons. These are both positive and negative. On the one hand, ACE inhibitors do not entirely prevent angiotensin II synthesis, which appears to have a particularly large non-ACE component. This enzyme, chymase, is particularly abundant in human vessels[61,62] and maybe in the heart, though this is controversial. On the other hand, cough and angioedema are believed to be due to accumulation of bradykinin and other non-angiotensin peptides.[63,64]

However, this in turn leads to a very important question concerning the mechanism of action of ACE inhibitors: how much do bradykinin and related peptides contribute to the therapeutic efficacy of the ACE inhibitors?[65,66] Furthermore, if angiotensin AT_1 receptors are blocked, what is the consequence of the unopposed activation of AT_2 receptors? Again, expression of these receptors is considerably higher in the human heart than in tissues from most other species, and it has been proposed that activation of this receptor will promote nitric oxide release, possibly through activation of the kinin system: in fact functionally similar to ACE inhibition.[67] In the short term, at least, the receptor antagonists do appear to improve hemodynamic parameters as well as symptoms.[68]

There have now been two full clinical trials comparing an ACE inhibitor and an AT_1 receptor antagonist in heart failure. The *ELITE* study[69] compared captopril and losartan in an elderly patient population, and suggested some advantage for the latter in terms of reduced all-cause mortality, incidence of sudden death and of hospitalization. However, the study was relatively small (722 patients) and the primary endpoint was, rather surprisingly, deterioration in renal function.

A follow-up study, ELITE II[70] compared captopril (up to 150 mg daily) with losartan (up to 50 mg daily), in over 3000 patients aged 60 years or over with moderate to severe heart failure. The primary endpoint was all-cause mortality and the secondary endpoints were sudden death or resuscitated cardiac arrest. The median follow-up period was approximately 18 months. There were no differences between the two groups in either primary or secondary endpoints, although there was a slight tendency for better outcomes in the captopril group. Losartan was, however, significantly better tolerated (9.7% patients withdrawals vs 14.7%, $p < 0.0001$).

Trials involving other AT_1 receptor blockers are also in progress. The RESOLVD study[71] has already been discontinued because of apparently worsening mortality in the can-

desartan as compared to the enalapril group. This may be a real effect or a statistical accident. In any case, there is clearly a great deal more to be learned about these drugs before their role is established.

Hyperaldosteronism: are ACE inhibitors sufficient?

Patients with heart failure have high levels of circulating aldosterone, sometimes resembling those seen in Conn's syndrome. ACE inhibitors have a variable and often modest effect on levels of this hormone. Aldosterone is now widely believed to have several harmful properties independent of angiotensin II: for instance, promoting magnesium and potassium loss, cardiac fibrosis and impaired vascular compliance, as well as increasing sodium and water retention.[23,72] It may be anticipated that ACE inhibitors would lower aldosterone levels, since the hormone is effectively the end-product of the renin-angiotensin system. In practice, there is often a disappointing response, and 'escape' may occur even after an initially promising result.[73]

A rational approach would then be to use spironolactone, an aldosterone antagonist, in addition to ACE inhibition. The RALES trial[30] has confirmed that this combination is not only safe but effective. Over 1600 patients were enrolled in the study and there was a 30% reduction in mortality over 2 years in patients on spironolactone 25–50 mg daily as compared to those on placebo but already on optimal treatment with an ACE inhibitor. There was also improvement in patients' NYHA class. There was very little hyperkalemia and virtually no significant hypotension.

ACE inhibitors and diastolic heart failure

It is increasingly recognized that many patients with clinical heart failure, perhaps as many as 20–40% of the total, have well-preserved systolic function. This is particularly true of the elderly.[74] Hypertension is probably the most frequent cause of diastolic heart failure and others include diabetes and amyloid. Although this has been, and to some extent remains, a controversial area, diagnostic criteria are now well established.[75] Given the wealth of trial data in patients with poor systolic function, it is striking that there is little comparable evidence for diastolic heart failure and therefore there has been comparatively sparse systematic review of the therapy.[76,77] However, evidence is now emerging that ACE inhibitors can favorably affect outcomes in patients where the ejection fraction is 0.40 or more.[78]

The use of ACE inhibitors: proposals

There is obviously a huge amount on information on the use of ACE inhibitors in coronary artery disease. Equally, there is much that is not known and which may be too difficult and too expensive to find out. The following are very much personal proposals based on current knowledge.

- ACE inhibitors are appropriate in all cases of heart failure, of all degrees of severity, unless specifically contraindicated.
- ACE inhibitors are indicated in survivors of MI if there is significant LV dysfunction, even without heart failure, again unless there is a specific contraindication. There

may be a reduction in the rate of reinfarction as well as less progression to heart failure. At present, recommending the use of ACE inhibitors in the presence of normal ventricular function is not so clear cut. It also remains to be determined whether very early introduction of these drugs (within 24 hours) is indicated.

- ACE inhibitors may also be indicated in patients who have undergone revascularization procedures, particularly if they have borderline left ventricular function.
- The HOPE study[47,48] has provided evidence for the use of ACE inhibitors in patients with proven ischemic heart disease with or without symptoms, and in diabetic patients with any additional cardiovascular risk factors. It is still a matter of some controversy whether this warrants routine use of the drugs in all these patient categories.
- ACE inhibitors should be used at adequate doses, that is those achieved in the trials and therefore based firmly on evidence.
- There is at present no direct clinical evidence, beyond the ELITE trials,[69,70] for the use angiotensin II antagonists in heart failure and LV dysfunction. However, their use may certainly be considered in patients responding to ACE inhibitors but with angioedema or severe cough.
- Spironolactone (and its eventual successors) is a rational supplement to ACE inhibition in suppressing the renin-angiotensin-aldosterone system in heart failure.
- There are no evidence-based guidelines on the use of ACE inhibitors in isolated diastolic dysfunction, though their use may be considered as a reasonable option depending on individual circumstances.

Conclusions

Information on actual drug use is, inevitably, outdated by the time it is published. However, there is general agreement that the use of ACE inhibitors in heart failure has been increasing since at least 1990. There is also a perception that usage in the UK has not been as widespread as in many other countries,[79] particularly in Western Europe, and in the United States. Even there, however, usage may not be optimal.[80,81] Much of this underutilization is attributable to anxieties about adverse effects, particularly symptomatic hypotension and renal impairment. In fact, 80–90% of patients are likely to tolerate ACE inhibitors without significant adverse effects. Clinicians should ensure that these effective, useful and generally safe drugs are used to their full potential.

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12

Angiotensin Receptor Blockers for Chronic Heart Failure and Acute Myocardial Infarction

John JV McMurray

Introduction

Two landmark clinical trials, CONSENSUS I and SOLVD-T, have shown, unequivocally, that angiotensin converting enzyme (ACE) inhibitors reduce all cause mortality in patients with chronic heart failure (CHF) and underlying left ventricular (LV) systolic dysfunction.[1,2] These and other trials have also confirmed that ACE inhibitors reduce morbidity, as manifest by hospital admission, in patients with CHF.[3]

A number of other key randomized, controlled trials have also shown that ACE inhibitors reduce the risk of all cause mortality and major clinical events (sudden death, reinfarction, heart failure) after myocardial infarction (MI).[4–6] These benefits are most clearly seen in patients with LVSD or clinical evidence of heart failure.[7] The ATLAS study has shown that higher doses of ACE inhibitor give greater morbidity/mortality benefits.[8]

Another drug known to block a component of the renin-angiotensin-aldosterone system (RAAS), spironolactone (an aldosterone antagonist), has also been shown in RALES to reduce mortality and morbidity in CHF, even when *added* to an ACE inhibitor.[9]

What, then, is the potential role of the newest agents available for RAAS inhibition, the angiotensin II receptor antagonists or blockers (ARBs), in CHF and acute MI?

ARB-ACE inhibitor comparison studies

Although, logically, the first question to ask of ARBs might be whether these new drugs are better than placebo, the first comparison actually made in a large scale trial was with an ACE inhibitor. The first of these, the ELITE trial, addressed tolerability, whereas, the hypothesis of the larger still ELITE II trial was that losartan would be more efficacious than captopril. The approach of the ELITE trials was based on the belief that, firstly, ARBs are more effective inhibitors of the RAAS than ACE inhibitors and, secondly, bradykinin, the breakdown of which is blocked by ACE inhibitors, is directly or indirectly responsible for cough and possibly other adverse effects of these agents.[10]

There is some scientific basis for the view that ARBs might be more efficacious than ACE inhibitors at blocking the RAAS. If it is accepted that ACE inhibitors bring about benefit through reducing the actions of angiotensin II, then there is some significance in the demonstration that angiotensin II generating pathways which bypass ACE and exist

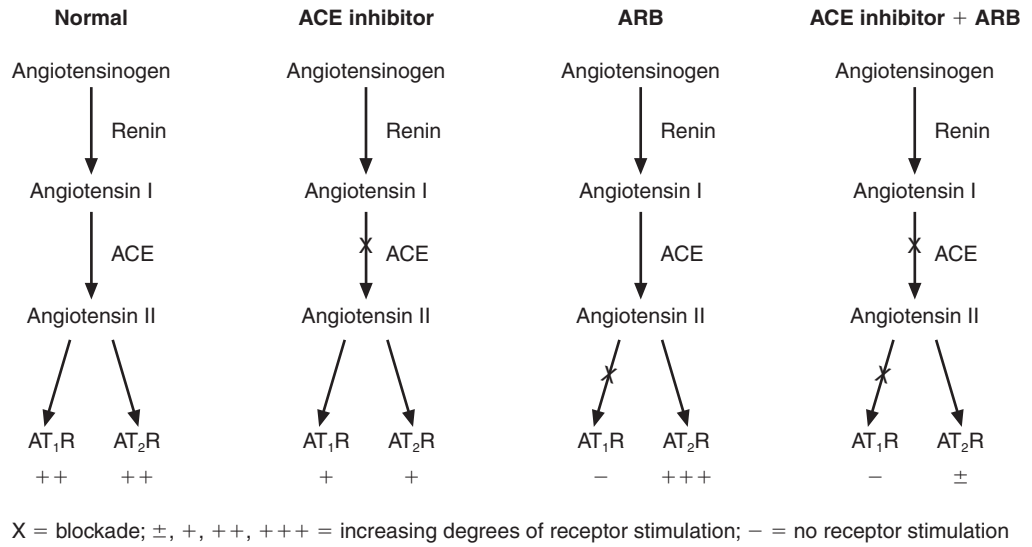

Figure 12.1
Different pharmacological profiles of action of ACE inhibitors and AT_1 receptor antagonists.

in human myocardium and arteries.[11–13] Clearly, these observations suggest that ARBs offer a potentially more effective means of inhibiting the actions of angiotensin II. Arguably, the ATLAS and RALES trials also support the view that more intense inhibition of the RAAS might be better.[8,9] This hypothesis, however, needs to be tested in one or more definitive morbidity/mortality trials, such as ELITE II (see below). Selective blockade of the AT, angiotensin II receptor subtype, with hyperstimulation of the unblocked AT_2 receptor (AT_2R) by displaced angiotensin II, is also more attractive, theoretically, than reduced stimulation of both receptor subtypes with an ACE inhibitor (Fig. 12.1). This is because the AT_2R *may* mediate biological actions which are the opposite of those that follow AT_1R activation (and, hence, potentially favorable in CHF). How have these hypotheses stood the test of clinical trials?

Tolerability: SPICE and ELITE

If ARBs are no more efficacious than ACE inhibitors, but are better tolerated, then there may be potentially substantial public health benefit to be gained. Although we do not yet know if ARBs are as efficacious as ACE inhibitors (see below), we do know ARBs are better tolerated. ARBs do not cause cough and do not seem to cause more of any other adverse effect than ACE inhibitors. Certainly, the SPICE trial found that candesartan was well tolerated by patients deemed to be ACE inhibitor-intolerant by their physician.[14] In the ELITE study, 20.8% of captopril-treated patients discontinued therapy because of an adverse event (excluding death) compared to 12.2% of losartan-treated patients ($p \leq 0.002$).[10,15] The more recent ELITE II study supports this finding, reporting that 14.5% of patients withdrew from captopril

because of adverse effects, compared to 9.4% from losartan ($p < 0.001$).[16,17]

Efficacy: ELITE, RESOLVD and ELITE II

The ELITE study reported the surprising finding that patients with CHF treated with losartan had a lower mortality than patients treated with captopril.[10,15] The trial was not designed to test this hypothesis and was too small to prove, with confidence, that ARBs have superior efficacy to ACE inhibitors. The RESOLVD study, comparing candesartan cilexitil (candesartan) to enalapril did not support the findings of ELITE.[18,19]

ELITE II was a large, prospective, properly powered, study that compared an ACE inhibitor (captopril) to an ARB (losartan). It was designed to test the hypothesis that losartan was more efficacious than captopril (Tables 12.1–12.3).[16,17] This hypothesis was not proven, that is, losartan was found not to be superior to captopril (Table 12.4), and the results cannot be used to test further hypotheses. ELITE II cannot tell us whether losartan is 'as good as' (equivalent to) captopril or, at least, 'no worse than' (not inferior) to captopril. These terms have strict statistical and regulatory definitions that the design and results of ELITE II do not fulfil.[20] Indeed, ELITE II cannot even confirm that losartan is superior to placebo.[21]

ARB-ACE inhibitor combination studies

The second question to be addressed by a major clinical trial, was whether ARB-ACE inhibitor *combination* therapy is better than ACE inhibitor monotherapy. The hypothesis underlying this approach is very different than that underlying the ELITE studies. Both hypotheses propose that ARBs are better inhibitors of the RAAS, however the combination therapy approach takes the view that bradykinin is 'good' rather than 'bad'.[22] This is because bradykinin may enhance the production of nitric oxide and possibly other vasoactive mediators, such as vasodilator prostanoids, in vascular and other tissues.[23–25] Bradykinin may also stimulate tissue plasminogen activator release from the endothelium and favorably influence coagulation/fibrinolysis balance.[26] Consequently, combination ARB-ACE inhibitor therapy may give both optimum RAAS inhibition and the putative benefits of bradykinin accumulation, through inhibition of its breakdown.

A number of relevant 'mechanistic' and 'pilot' clinical studies preceded the first definitive large-scale trial, Val-HeFT, to explore this hypothesis.

Smaller studies

There is conflicting clinical evidence that some of the effect of ACE inhibitors may be due to their blocking effect on bradykinin breakdown. Some studies in hypertensive individuals and healthy subjects, using a selective bradykinin inhibitor, have supported such an action, although another in heart failure does not.[23–25] These mechanistic findings are supported by some clinical observations. Baruch et al studied the immediate and 4-week hemodynamic and neurohumoral effects of placebo and valsartan, either 80 mg or 160 mg twice daily, added to conventional therapy (including an ACE inhibitor) in patients with CHF.[27]

	ELITE II[16,17]	*Val-HeFT*[22]	*CHARM*[27]
Number of patients	3152	5010	7601*
Entry criteria	• ≥60 yr (85% ≥65) • NYHA Class II–IV • ≥70% IHD • LVEF ≤0.40 • No ACE-I/ARB within 3 months • ≤25% beta-blocker	• NYHA Class II–IV • LVEF <0.40 and LVIDD >2.9 cm/m^2 • usual background therapy (most ACE-I)	NYHA Class II–IV (i) LVEF ≤0.40 ACE-I intolerance arm (n = 2028) (ii) LVEF ≤0.40 ACE-I/ARB combination arm (n = 2548) (iii) LVEF >0.40 arm (n = 3025)
Treatment groups	Captopril vs losartan	Placebo vs valsartan (background ACE-I)	Placebo vs candesartan – no ACE-I (I); placebo vs candesartan-all background ACE-I (II); placebo vs candesartan – optional background ACE-1 (III)

LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
ACE-I = angiotensin converting enzyme
IHD = ischemic heart disease
LVIDD = left ventricular internal dimension

Table 12.1
ARB trials in CHF: number of patients and main inclusion criteria.

Compared to placebo, high-dose valsartan reduced pulmonary capillary wedge pressure and systolic blood pressure acutely and after 1 month's treatment. Valsartan, at both 80 mg and 160 mg twice daily, significantly reduced aldosterone at 4 weeks.

Not all studies have supported these findings, however, and there remains the nagging doubt that similar benefits might be obtained by using a bigger dose of ACE inhibitor, rather than adding an ARB.[28–30] However, Hamroff et al reported a small but impressive 6-month randomized trial in which patients with moderately severe CHF were randomized to placebo or losartan 50 mg once daily.[31] All were receiving full conventional therapy, including an ACE inhibitor given in an adequate dose (e.g. the mean daily

	Non-inferiority	*Superiority*		
	ARB ≤ ACE-I	*ARB > placebo*	*ARB > ACE-I*	*ARB + ACE-II > ACE-I*
ELITE II[16,17]	no	no	yes no (RR 25%, P 90%)[C]	
Val-HeFT[22]	no	no	no	yes (RR 20%, P 90%)[D]
CHARM[27]	no	yes (LVEF ≤ 0.40[A] (RR 18%, P 94%) LVEF > 0.40[B] (RR 18%, P 86%)	no	yes (RR 18%, P 90%)[E]

≤ not significantly inferior to
RR = risk reduction
P = power, i.e. power of study to detect risk reduction (e.g. Val-HeFT has a 90% power to detect a 20% relative risk reduction in mortality with valsartan compared to placebo)
[A]assuming an annual placebo group event rate of 24%
[B]assuming an annual placebo group event rate of 13%
[C]assuming a captopril group annual mortality rate of 9.4%
[D]assuming placebo group annual mortality rate of 12%
[E]assuming an annual placebo group event rate of 18%

Table 12.2
ARB trials in CHF: hypotheses tested.

dose of enalapril was 32 mg). The primary endpoints were exercise capacity and New York Heart Association (NYHA) class. Both improved significantly and losartan was well tolerated.

In the RESOLVD pilot study the combination of enalapril and candesartan had significantly more favorable effects on the LV remodelling than either monotherapy.[18,19] Clinical outcome was not, however, better in the candesartan-enalapril combination group. The hypothesis that combination therapy is the optimum had, therefore, to be tested in a large-scale morbidity-mortality trial.

The Valsartan Heart Failure Trial

The key features of the design of Valsartan Heart Failure Trial (Val-HeFT) are shown in Tables 12.1 and 12.2.[22] Professor JN Cohn, from the University of Minnesota, presented the demographic characteristics and preliminary results of Val-HeFT at the 73rd Scientific Sessions of the American Heart Association (AHA, New Orleans, November 2000) and the subsequent information on Val-HeFT has been obtained from that presentation.

The principal hypothesis tested by Val-HeFT was that, adding valsartan to conventional therapy (including an ACE inhibitor and beta-blocker, where appropriate) would improve clinical outcome. The co-primary

	ELITE II[16,17]	*Val-HeFT*[31]
Number of patients	3152	5010
Mean age (years)	71	63
Males (%)	70	80
NYHA Class (%)		
II	52	62
III	43	36
IV	5	2
Left ventricular ejection fraction (%)	31	27
Concomitant diagnoses (%)		
Coronary etiology*	79	57
Hypertension	49	–
Atrial fibrillation	30	12
Diabetes mellitus	24	24
Drug treatment (%)		
Diuretic	78	86
ACE inhibitor	–**	93
Cardiac glycoside	50	67
Beta-blocker	22	34

Key
*'history of ischemia' in ELITE II
**patients randomized to either losartan or captopril (23% of patients had received prior ACE inhibitor)

Table 12.3
Clinical characteristics of patients enrolled in ELITE II and Val-HeFT.

endpoints were firstly mortality (all cause) and secondly mortality or morbidity. Morbidity included hospitalization for CHF, resuscitated sudden death and administration of intravenous inotropic or vascular therapy for CHF for ≥4 hours.) Secondary endpoints included change in NYHA class, signs and symptoms of CHF, LV ejection fraction and quality of life. Val-HeFT randomized 5010 patients, the clinical characteristics of whom are summarized in Table 12.3.[32] The average follow-up time was approximately 1.9 years.

The principal results, as presented at the AHA, are shown in Table 12.5. Valsartan did not reduce mortality but did significantly reduce the combined morbidity-mortality endpoint by approximately 13% ($p = 0.009$). This effect was principally due to a substantial 27% reduction in CHF hospitalization (see Table 12.5, $p = 0.00001$). There were similarly impressive and significant improvements in the other secondary outcomes presented.

Analysis

At face value, Val-HeFT would appear to be a

Endpoint	*Number of patients*		*Hazard ratio (95% CI)*	p-*value*
	losartan n = 1578	*captopril n = 1574*		
All-cause mortality	280 (17.7%)	250 (15.9%)	1.13 (0.95–1.35)	0.16
Sudden death or resuscitated cardiac arrest	142 (9.0%)	115 (7.3%)	1.25 (0.98–1.60)	0.08
Combined total mortality or hospitalization for any reason	752 (47.7%)	707 (44.9%)	1.07 (0.97–1.19)	0.18
Hospital admissions (all causes)	659 (41.8%)	638 (40.5%)	1.04 (0.94–1.16)	0.45

Table 12.4
ELITE II endpoints.[16,17]

Endpoint	*Number of patients*		*Risk ratio (95% CI)*	p-*value*
	valsartan n = 2511	*placebo n = 2499*		
All-cause mortality	495 (19.7%)	484 (19.4%)	1.02 (0.90, 1.15)	0.8
Combined all cause mortality + morbidity	723 (28.9%)	801 (32.1%)	0.87 (0.79, 0.96)	0.009
HF hospitalizations	349 (13.9%)	463 (18.5%)	0.73 (0.63, 0.83)	0.00001

Based on data presented by Professor JN Cohn to AHA meeting, 15 November 2000.

Table 12.5
Val-HeFT: endpoints (preliminary).†

'positive' trial, with statistically significant improvements in pre-specified co-primary and secondary endpoints. Unfortunately, however, the story may not be that simple. Professor Cohn went on to present detailed sub-group analyses which appeared to raise important questions about the overall findings of Val-HeFT. Firstly, outcomes in the small minority (7%) of patients not taking on ACE inhibitor at baseline were compared to those in patients taking an ace inhibitor. The former group had an approximately 45% reduction in

mortality/morbidity compared to a 12% in the latter. In other words, this analysis raises the possibility that most of the benefit in the overall trial can be explained by a particularly large effect in patients not receiving an ACE inhibitor.

To complicate matters further, patients receiving a beta-blocker at baseline (about 35%) were compared to those not. The hazard ratio for the mortality/morbidity endpoint in patients taking a beta-blocker was 1.15 (i.e. there was a trend for such patients to do worse on valsartan) compared to 0.78 in those not on a beta-blocker. In other words, this raised the possibility, confirmed by further analysis, that 'triple neurohumoral blockade' (ACE inhibitor, beta-blocker, ARB) has no advantage over double blockade and may even be disadvantageous.

It must be emphasized that sub-group analysis of this type is fraught with danger, can be very misleading and should only be regarded as generating hypotheses.[33] Unfortunately, however, the beta-blocker sub-group analysis has attracted much attention because beta-blockers, along with ACE inhibitors, are not regarded as mandatory treatment for CHF. The issue is further confounded by a directionally apparently similar beta-blocker interaction in ELITE II (captopril-treated patients did better than losartan-treated patients if receiving beta-blocker therapy at baseline).[17]

Following both ELITE II and Val-HeFT, the evidence on ARBs remains unclear. From a purist perspective, Val-HeFT does suggest that adding an ARB to conventional therapy reduces morbidity (CHF hospitalization). How much attention should be paid to sub-group analyses is very debatable. Any firm conclusion cannot be reached until at least full publication of the Val-HeFT results. It must be reiterated that only preliminary data are available at the time of writing. Analysis of the neurohumoral and left ventricular remodelling data from this study should give additional insight into the issues raised above.

The CHARM program

A more complete picture will follow completion of the candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program completes.[34] This three-study program is now ideally poised to address some of the remaining uncertainty about ARBs.[34] In particular, CHARM includes a study in patients not taking an ACE inhibitor (Study 0003) (see below). In addition, in the ACE-I plus ARB combination arm (Study 0006), more patients are receiving a beta-blocker at baseline than in Val-HeFT (55% versus 35%) and all are taking an ACE inhibitor, allowing further exploration of any potential ARB-beta blocker interaction.

ARB-placebo comparison studies

Remarkably, it has been generally assumed that ARBs are an effective treatment for CHF (i.e. superior to placebo) even though there are very few data to support this assumption. Clearly, the widely held opinion that ARBs are efficacious in CHF is based on the view that RAAS inhibition is beneficial. This perception is, in turn, based on the belief that ACE inhibitors and spironolactone exert their effect in this way. While almost certainly true, at

	Placebo	*Active*	*Odds ratio (95% CI)*	p *value*
Candesartan	11/606	20/1,287	0.85 (0.39, 1.99)	0.810
Losartan	13/274	11/616	0.37 (0.15, 0.90)	0.027
Valsartan	49/181	32/185	0.56 (0.33, 0.96)	0.033
Combined	73/1,061	63/2,088	0.56 (0.38, 0.81)	

Data derived from Sharma et al,[38] Erdmann, et al[39] and unpublished data from Val-HeFT.

Table 12.6
Meta-analysis of existing ARB-placebo comparisons in CHF (mortality).

least in part, even the most apparently obvious hypotheses require testing.

Smaller studies

ARBs, like ACE inhibitors, have favorable acute and chronic neurohumoral and hemodynamic actions in CHF.[35,36] There are, however, remarkably few data showing any clinical benefit of ARBs over placebo. STRETCH has shown that, compared to placebo, one of these agents, candesartan cilexetil, can improve exercise tolerance in CHF in a dose-dependent manner.[37] This has not, however, been a consistent finding in all studies (there are two fairly large, unpublished, exercise studies that show no benefit of losartan over placebo. Meta-analyses of relatively small trials with losartan and candesartan have, however, suggested that ARBs might improve clinical outcomes when compared to placebo.[38,39] Data from the Val-HeFT subgroup not treated with an ACE inhibitor adds more support to the view that ARBs are more efficacious than placebo (Table 12.6).

However, no prospective randomized, placebo-controlled trial has, to date, tested the hypothesis that ARBs are superior to placebo in terms of morbidity-mortality or mortality endpoints in CHF. One such study is currently underway: one of the component trials of the CHARM programme (see Tables 12.1 and 12.2).[34]

A wider role for RAAS inhibition in CHF?

The emergence of a new class of drug for RAAS inhibition also presents the opportunity to test additional questions not formally tested in previous trials with ACE inhibitors. One pressing issue in clinical cardiology is the treatment of CHF in patients with preserved LV systolic function, who make up perhaps a third of all patients with CHF and who also have an increased morbidity and mortality.[40,41] Although LV ejection fraction measurements were not required for entry into either the CONSENSUS-1 or Val-HeFT studies, these trials are generally considered to have

recruited patients with LV systolic dysfunction.[42,43]

It is possible that RAAS inhibition might also be of benefit in patients with CHF and preserved LV systolic function. These patients are treated with diuretics which may be expected to cause RAAS activation.[42] Many are hypertensive, diabetic and have LV hypertrophy, comorbidies that might be expected to respond favorably to RAAS inhibition, especially in the light of the recently reported Heart Outcomes Prevention Evaluation (HOPE) study.[45,46] Once more, of course, this is a hypothesis that needs to be tested in an appropriately designed clinical trial. Two trials are under way: one is with the ACE inhibitor perindopril (PEP-CHF)[47] and one is a component trial of the CHARM programme.[34] Another trial, with irbesartan, is at an advanced stage of planning.

ARB myocardial infarction (MI) trials

Two trials are under way in patients with acute MI: OPTIMAAL and VALIANT, as outlined in Tables 12.7 and 12.8.[48,49] OPTIMAAL is similar to the ELITE trials in comparing losartan to captopril.[48] The patients randomized are high-risk survivors, who are broadly similar, but not identical, to those recruited into the seminal ACE inhibitor post-MI trials (i.e. SAVE, AIRE, TRACE). OPTIMAAL is sufficiently large to have a 95% power of showing a 20% relative reduction in the risk of death with losartan compared to captopril.[48]

VALIANT has a more complex design, with three treatment groups (captopril, valsartan and their combination), and is powered not just to test for superiority but also for non-inferiority.[49] As a consequence, the

	OPTIMAAL[48]	*VALIANT*[49]
Number of patients	5476	14 814
Entry criteria	≥50 years anterior Q wave MI *or* new LBBB or signs of heart failure *or* LVSD/dilation	LVSD and/or signs of heart failure
Treatment groups	captopril losartan	captopril valsartan captopril + valsartan

LBBB = left bundle branch block
LVSD = left ventricular systolic dysfunction

Table 12.7
ARB trials post-MI: design.

	Non-inferiority	*Superiority*	
	ARB ≤ ACE-I	*ARB > ACE-I*	*ARB + ACE-I > ACE-I*
OPTIMAAL[46]	yes*	yes** (20%, P 96%)	no
VALIANT[47]	yes (2.5%, P 88%) (0%, P 74%)	yes (17.5%, P 95%) (15%, P 86%)	yes (17.5%, P 95%) (15%, P 86%)

≤ = not significantly inferior to
*revision of protocol as published,[43] further details not available
**assuming a captopril group annual mortality of 17%

Table 12.8
ARB trials in post-MI: hypotheses tested.

patient entry criteria must exactly mirror those of the reference trials, SAVE, AIRE and TRACE.[7] Amongst the questions that VALIANT can address is whether ARBs have similar efficacy to ACE inhibitors (non-inferiority) but are better tolerated. VALIANT will, of course, also show whether combination ACE inhibitor-ARB treatment is superior to ACE inhibitor monotherapy in the post-MI setting.

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13

Cardiovascular Disease in the Elderly

Peter O'Kane and Graham Jackson

Introduction

Cardiovascular diseases are the commonest cause of morbidity and mortality in those aged over 65. The most frequent manifestations include ischemic heart disease, cardiac failure, atrial fibrillation and hypertension. The burden of cardiovascular disease caused by disability and dependency is costly to society in terms of health and social resources. Approximately 20% of Europeans are currently over the age of 65 years and, as the population ages further, the size of this management problem will increase.

Aging itself produces a number of physiological changes that can sometimes be difficult to distinguish from age-related pathology. The same disease process may present differently in a 65-year-old compared to in an individual aged over 80. Similarly, treatments used in patients aged 65–75 years may not always be appropriately applied to patients aged 75–85 years. This group is usually excluded from clinical trials. The aging process may have modified cardiovascular structure and function sufficiently to alter the pharmacologic response. A sound knowledge of the normal physiology of aging is thus essential. It is also necessary to view a patient's 'biological' age rather than advising or denying therapy based solely on their chronologic age.

As the risk of cardiac disease increases with age, the benefits of cardiovascular factor risk modification, especially secondary prevention, may become more cost-effective in the elderly than in the younger population. In terms of pharmacologic management, the relatively minor differences in pharmacokinetics and pharmacodynamics between young and old should not be an excuse for under-prescribing in the elderly. The aim of treating cardiovascular disease in the elderly is to improve quality of life, promoting a more active lifestyle and thereby avoiding feelings of dependency. Prescribing in the elderly is hazardous – the 'RAMPS' approach is sometimes helpful (Table 13.1).[1] Good prescribing habits are paramount (Table 13.2).

This chapter aims to highlight key issues in modern cardiovascular medicine in the elderly, with an emphasis on pharmacologic treatments and new areas of research.

Age-related physiological changes

There are a number of anatomical changes that occur to the cardiovascular system during aging (Table 13.3). In the heart there is increased fibrosis and calcification of the valve rings, particularly the mitral annulus and the

Reduced body reserve for dosing, such as the expected decrease in renal and hepatic function with age

Atypical presentation of any illness is possible, including heart disease

Multiple pathologies, usually coexisting

Polypharmacy makes further prescribing hazardous

Social adversity

Reproduced with permission from Livesley 1997.[1]

Table 13.1
The 'RAMPS' approach.

- Increased fibrosis and calcification of valve rings
- Degeneration of sinus node pacemaker and other conducting tissue
- Thickened left ventricular wall reduces left ventricular cavity size
- Loss of left ventricular compliance with subsequent left atrial hypertrophy may lead to AF and diastolic dysfunction
- Impaired peripheral vessel compliance and coronary arteries more susceptible to CAD

Table 13.3
Physiology of aging.

aortic valve.[2] This is usually not of any functional or hemodynamic significance, although there is some evidence that aortic valve sclerosis may significantly increase cardiovascular and total mortality, even without outflow obstruction.[3] The prevalence of aortic valve sclerosis in those aged over 65 years may be up to 26%, increasing to 37% in those over 75. In contrast, the prevalence of aortic valve stenosis is 2% at age 65, increasing to 2.6% at 75.[3]

The conductive tissues of the myocardium are also affected by age. By the age of 75 years there remain only 10% of the sinoatrial cells present at age 20.[4] Muscle cells are reduced with mild increases in fibrous tissue in the

Monotherapy	using one drug to treat two conditions
Polypharmacy avoidance	cessation of unnecessary drugs
Slow titration of dose	small initial doses, increased slowly and at longer intervals
Anticipate interactions	especially with warfarin, amiodarone and digoxin
Monitoring	especially drugs with narrow therapeutic range, e.g. digoxin
Alert to side-effects	dose-dependent and idiosyncratic
Pill boxes	aid compliance

Table 13.2
Good cardiovascular prescribing in the elderly.

internodal tracts. Atrioventricular node defects are more common in the elderly. The prevalence of right bundle branch is 8% and left bundle branch block is 5%.

The left ventricular wall thickens independent of any increase in blood pressure, caused by individual myocyte hypertrophy. Absolute myocyte numbers reduce as a result of fibrosis and cell atrophy. Their ability to relax is altered by impaired calcium release and reuptake from the contractile proteins and sarcoplasmic reticulum.[5,6] The left ventricular cavity size is subsequently reduced and is less compliant as a result of deposition of collagen, lipid and amyloid.[2]

The increase in cardiac stiffness impedes 'passive' ventricular filling that occurs in the early phase of diastole. Consequently, in the elderly, there is a much larger contribution from atrial contraction which can be responsible for up to 40% of ventricular filling, compared to 15% in young adults. There is often subsequent hypertrophy of the left atrium as it attempts to overcome the increased resistance to ejection. This in turn increases the tendency for atrial ectopic beats as foci for atrial dysrhythmias. This effect may account for the increased incidence of atrial fibrillation in the elderly and explain how the lack of co-ordinated atrial activity can precipitate pulmonary and systemic congestion, even in the presence of normal left ventricular systolic function. The non-compliant ventricle is also sensitive to small increases in intravascular volume, which can similarly lead to congestive cardiac failure in elderly patients.

Aging also impairs peripheral and central arterial wall compliance with an increase in stiffness which results from proliferation of collagen cross links, smooth muscle hypertrophy, calcification, and loss of elastic fibers.[4] Increased resistance to left ventricular ejection (an increase in afterload) occurs and often results in left ventricular hypertrophy, which further worsens diastolic dysfunction. Increased vascular stiffness may explain the association of isolated systolic hypertension, which occurs more commonly in the elderly population. Age-related decreases in capillary density and coronary reserve may cause myocardial ischemia and thus increase further diastolic abnormalities in the absence of coronary atherosclerotic disease.[5]

With age, the coronary arteries become more susceptible to atherosclerosis, so that the elderly generally have more severe, diffuse and calcific coronary artery disease that particularly involves the left main stem. The vascular smooth muscle cells lose their ability to break down low-density lipoproteins (LDL): resultant LDL accumulation within the endothelium promotes endothelial dysfunction that can alter laminar blood flow. With age there is also an increase in procoagulant factors with reduced anticoagulant factors in the blood. In the elderly, the classical Virchow's triad thus develops and results in enhanced thrombogenicity.

After excluding patients with coronary artery disease and hypertension, studies show that there is little change in left ventricular systolic function with increasing age, although cardiac output may decrease in parallel with a reduction in lean body mass. The determinants of cardiac output which may be influenced by age include heart rate, preload and afterload, skeletal muscle performance, and neurohormonal regulation.

The elderly cardiovascular system is less able to compensate for circulatory changes. The baroreceptor reflex is blunted which is manifest by a reduction in the heart rate

response to hypotensive stimuli. There is reduced ability of the kidneys to maintain intravascular volume and electrolyte balance because of a decline in glomerular filtration rate (8 ml/min per decade), coupled with a tendency for salt-wasting through lower levels of renin, angiotensin II and aldosterone and a higher level of atrial natriuretic peptide.[7] In addition, there is a reduced sense of thirst in the elderly following water deprivation.[8] During acute illness involving intravascular fluid depletion and in response to diuretic or vasodilating therapy, there is a greater risk of hypotension in elderly subjects

Coronary artery disease

Epidemiology

The prevalence of obstructive coronary artery disease (CAD) rises dramatically with increasing age – up to 50% of men are affected by severe narrowings at 60 years.[9] Age is an independent risk factor for CAD (Table 13.4). Angina affects approximately 15% of adults aged over 65 years and acute myocardial infarction (AMI) affects 11% of the 65–69 age group and 18% of 80–84 year-olds.[9] Of deaths attributed to AMI, 60% are in patients over 75 years.[10] One post-mortem study in patients over 90 years of age discovered that 70% had one or more occluded coronary arteries, although this had only been detected clinically in approximately half of these patients.[11]

- Age is independent risk factor for CAD
- A large number of elderly patients with CAD are undiagnosed
- An increasing number of elderly patients have coronary angiography but the level of use is less than expected for the extent of disease
- Absolute risk reduction from thrombolysis post-AMI is highest for older patients
- Beta blockers and ACE inhibitors significantly reduce mortality post-AMI but are underused in the older population
- Low molecular weight heparin can be used safely in ACS but the role of glycoprotein IIb/IIIa inhibitors is less certain
- Secondary prevention of CAD including statin therapy should be considered in the majority of elderly patients
- PCI should be available to suitably selected patients but successful outcome may be limited by technical difficulties in this age group
- CABG may have higher short-term risks but can offer excellent longer-term benefits even in patients over 80 years

Table 13.4
Coronary artery disease and aging.

Clinical presentation

In the elderly, the presence of chest pain is most commonly associated with obstructive CAD. However, an elderly patient is as likely to present with an AMI with symptoms of shortness of breath in the absence of pain. Indeed, non-specific symptoms are common including confusion, syncope, vertigo and epigastric pain. Silent ischemia, an impaired sensitivity of pain, is also common in the elderly as exemplified from the Framingham study where 42% of males aged 75–84 years with AMI were asymptomatic or unrecognized, compared to 18% of men with AMI aged

45–54 years.[12] There are some studies which show that unrecognized AMI may occur in as many as 68% of patients over 64 years[13] and 60% of patients over 80 years.[14] Elderly women have a higher tendency to suffer unrecognized AMI; also, patients who are smokers, those with hypertension and those who lack a history of exertional angina are at higher risk.[15,16] A silent infarction can also explain why a diabetic patient suddenly loses blood glucose control for no obvious reason.

Investigations

Typical investigations used in younger patients for ischemia can be applied to the elderly. However, even in the absence of cardiac disease, the standard 12-lead ECG may be abnormal in the elderly. Shifts in the frontal plane axis, intraventricular conduction delay and reduced QRS voltage may simply reflect normal aging and can make the diagnosis of AMI more difficult. In the elderly, the proportion of patients with the classical ECG abnormalities of ST elevation or Q waves varies from 25% to 40%.[17,18]

In those in whom the diagnosis of CAD is uncertain, exercise tolerance testing can be performed. Bicycle testing is often better tolerated than treadmill testing, although elderly patients often fail to achieve over 85% of their maximum target heart rate and comorbidity often limits the test. Pharmacologic stress testing using dobutamine with echocardiographic imaging and dipyridamole or adenosine stress with thallium-201 or technetium-99 perfusion scan imaging may be useful but can not be undertaken if the patient has uncontrolled hypertension. Sensitivity and specificity of myocardial perfusion scans have improved with the use of single-photon emission computed tomography (SPECT). Positron emission tomography (PET) is useful in identifying hibernating myocardium which would strengthen a case for surgical or percutaneous revascularization.

Coronary angiography is the gold standard and, in addition to its diagnostic potential, offers the chance of revascularization. In the US, the number of patients undergoing this procedure who are over 75 years has increased from 7% in 1973 to 21% in 1993.[17] Despite this increase, the elderly are not offered enough coronary angiography to match the extent of disease in this population. In acute presentation of ischemia, PRAIS UK data have demonstrated that the risk of death was highest in those who were older, had ST segment changes or T wave inversion, while the majority of cardiac catheterizations were performed in lower risk, mainly young patients.

Management

The management of CAD is dependent upon the manner in which it presents. Unstable angina and evolving myocardial infarction share the same underlying pathophysiologic mechanisms and as such are generally components of the 'acute coronary syndrome' (ACS). The progression to AMI with characteristic electrocardiographic ST segment elevation in a proportion of these patients reflects the relative degree of atherosclerotic plaque erosion and rupture and extent of consequent thrombosis and distal vessel embolization. As with younger patients, the management of ACS can be subdivided into those patients with AMI who have persistent electrocardiographic ST elevation and those with non-persistent ST elevation.

Acute myocardial infarction

The primary objective in AMI, in addition to symptom relief, is to promote early reperfusion of the infarcted myocardial territory with the use of thrombolytics or by percutaneous coronary intervention (PCI). In older patients, this goal can be more difficult to achieve not just because of atypical presentation. Late presentation, for example, is critical since the time window for successful thrombolysis is 12 hours following onset of chest pain, given that this corresponds to acute occlusion of a coronary artery. One study revealed that in a group of patients aged over 80, the delay in calling paramedics was more than 6.5 hours compared to 3.9 hours in younger patients.[18] In treating symptoms of chest pain, intravenous nitrates can be titrated to systolic blood pressure (>100 mmHg) and opiate analgesia can be used, but in smaller doses to prevent respiratory depression. Unfortunately, elderly patients have been excluded from up to 60% of the major clinical trials for treatments of AMI.[17] However, some of the large studies recruited patients irrespective of age. In suspected AMI, all patients should receive aspirin 300 mg immediately followed by 75 mg daily unless absolutely contraindicated. The benefit from aspirin was greatest in the patients over 70 years in ISIS 2.[19] This should be followed by prompt thrombolysis when AMI is confirmed.

Thrombolysis

The results of thrombolysis from trials ISIS 2[19] and GISSI 1[20] (which had 35% patients over 65 years and 10% patients over 75 years), clearly demonstrated that the absolute reduction in mortality was in fact greatest in the older patients. There was an age-related trend towards an increased incidence of strokes in ISIS 2 for both treated and untreated patients. However, streptokinase attained a reduction in risk of death without any significant increase in stroke in all patients including those over 70 years.[19] The incidence of intracranial hemorrhage in elderly AMI patients is higher in those treated with recombinant tissue plasminogen activators (rtPA) than in those treated with streptokinase.[21] Risk factors for development of cerebral bleeding after thrombolytic therapy are low body weight (under 65 kg), female sex, hypertension and the use of oral anticoagulants prior to thrombolysis.

Compared to streptokinase, alteplase an rtPA administered in a 'front-loaded approach' over 90 minutes offers a superior reperfusion rate associated with a lower 30-day mortality.[22] However, the increased risk of stroke does restrict its use in the elderly. Bolus thrombolytics have been studied, including reteplase given as a double bolus 30 minutes apart but proved no more efficacious than alteplase in terms of mortality and reduction of adverse events.[23] A study of single bolus tenecteplase, a genetically engineered variant of alteplase, showed equivalence to alteplase for 30-day mortality in 16 504 patients with AMI where 12.5% were over 75 years of age.[24] Despite better fibrin specificity with tenectplase, the frequency of cerebral hemorrhage was similar between the two treatment groups. Patients treated with tenectplase, however, had a lower incidence of non-cerebral bleeds and less need for transfusion, which may make single-bolus thrombolysis safer in the elderly.

Beta-blockers and ACE inhibitors

Early beta-blockade convincingly reduces mortality in patients of all ages post-AMI.[25]

However, there appears to be a reluctance to prescribe beta-blockers to the elderly. This was demonstrated in an eight month medical records study of 201,752 patients discharged following AMI, where 35% were aged 75–84 years and nearly 12% were over 85.[26] Overall, beta-blockers were prescribed to 34% of the study population, but to only 27% of those over 84 years. Patients were followed up for 2 years and relative and absolute risk of death calculated for those who received or did not receive beta-blockers at hospital discharge. In patients without complications, the relative risk reduction of beta-blocker therapy was 40%, which is better than the reduction seen in randomized trials with beta-blockers post-AMI. In patients over 80 years the relative risk reduction was reduced (at 32%) and there was an absolute benefit similar to or greater than that in patients with no specific risk factors since their mortality rate was substantially higher. Thus, it is unfortunate that the elderly patient, with most to gain from beta-blockers post-AMI, escapes treatment.

ACE inhibitors should be given to patients who are hemodynamically stable post-infarction within 24 hours where there is evidence of left ventricular failure or in those with large anterior AMI. Unfortunately, they too are often under-prescribed in the elderly after an AMI. An observational study, around the time of publication of the SAVE and AIRE studies, looked at 5433 post-AMI patients over 65 years of age without contraindication for ACE inhibitors.[27] Of the 3528 patients who had their left ventricular ejection fraction (LVEF) determined, 1228 had LVEF $< 40\%$, but only 45% of these actually received an ACE inhibitor on hospital discharge.

Evidence from the ELITE II study suggests that prescription of ACE inhibitors or beta-blockers has not improved.[28] Of the 3152 patients (mean age 71.5 years and mean LVEF 31%) entered into the study, only 23% had previously used an ACE inhibitor and 24% a beta-blocker. In addition, 50% were on digoxin, which has no mortality benefit as will be discussed in the section on cardiac failure.

ACS with non-persistent electrocardiographic ST elevation

The goals in the management of non-persistent ST elevation ACS are to stabilize the unstable coronary artery plaque, to relieve symptoms and to identify patients who are at high risk of progressing to AMI and its complications, in particular death. The criteria for categorization of high risk include recurrent ECG ischemia (such as ST segment depression), elevated troponin levels, hemodynamic instability, major arrhythmias (such as ventricular tachycardia) and post-infarct angina.[29] The initial treatment therefore includes aspirin, analgesia, anti-anginal therapy with intravenous nitrates and beta-adrenoceptor blockers, anticoagulation with heparin and, more recently, the use of intravenous platelet glycoprotein IIb/IIIa receptor antagonists.

Heparin

Unfractionated heparin has been used traditionally in patients with unstable angina, despite, there being no large-scale clinical trials that demonstrate benefit. A meta-analysis of the effect of heparin added to aspirin in patients with unstable angina showed a risk reduction in death or AMI of 33%, but the confidence interval was 0.44–1.02.[30] The pharmacologic profile of intravenous heparin is less predictable than that of the more recently developed low molecular weight heparins. These have the advantage of subcutaneous

administration which may allow potential longer term use without immobilization. The low molecular weight heparins have proved more efficacious than placebo and at least as effective as unfractionated heparin in reducing death and AMI, following trials in over 10 000 patients with unstable angina when used in the acute phase.[31,32] Longer term use has less convincing evidence, with an excess of major bleeds occurring.[33,34] Currently the low molecular weight heparins, dalteparin and enoxaparin, are licensed for use in ACS in the UK.

Glycoprotein receptors

Activated glycoprotein IIb/IIIa receptors on platelets connect with fibrinogen to form bridges between activated platelets, so propagating thrombus formation. The use of glycoprotein IIb/IIIa receptor inhibitors in ACS is increasing but there is scepticism amongst many physicians concerning the absolute benefits. Oral agents have no role and tend to increase mortality in the trials so far undertaken.[35] Intravenous agents do have mortality benefit and those licensed in the UK include abciximab (a monoclonal antibody), eptifibatide (a cyclic peptide) and tirofiban (a non-peptide). The benefit would appear to be in patients who are identified as high risk (particularly with elevated troponin) and who are inevitably destined to undergo coronary angiography and potential PCI. The average patient age in these studies was less than 65 years and thus this therapy cannot necessarily be recommended for elderly patients. There is an increased risk of bleeding and a potential risk of thrombocytopenia. However, used in selected patients as a 'bridge' to the catheter lab, glycoprotein IIb/IIIa receptor inhibitors may reduce future events.

Percutaneous coronary intervention

The use of primary percutaneous transluminal coronary angioplasty (PTCA) for AMI has been shown to be superior to thrombolysis, with lower mortality and reduced strokes in patients over 65[36] and, in a small study, in those over 80.[37] However, this service is not readily available to most patients and, even in the global centers of excellence, primary PTCA is rarely available on a 24-hour basis.

Patients with ACS who have high risk factors, including ischemia or post-infarct angina, should be referred for coronary angiography with a view to PCI. Symptoms refractory to maximal tolerated medical therapy should also be considered for revascularization by PCI. In high risk patients, there is evidence for an early invasive strategy (revascularization within 7 days of presentation), as opposed to a non-invasive approach where coronary angiography could be available at a later stage. The early invasive arm of the Fragmin and Fast Revascularization during Instability in Coronary Artery disease (FRISC II) study demonstrated a 22% risk relative reduction after 6 months compared to the non-invasive arm in 2457 patients with ACS treated with dalteparin or placebo.[38] The benefit was most marked in men over 65 years since they had high overall mortality risk.

Although offering excellent symptom control, there is no evidence to suggest prognostic superiority of PCI.[39] Clinical success decreases with increasing age, and with less-sustained end results. This may be due to more diffuse atheromatous disease, tortuous vessels or greater vessel calcification, which increases the need for stenting. The use of intra-coronary artery stents in the elderly population is contentious. The National Institute of Clinical

Excellence recently recommended an overall increase in the use of stents, particularly in elective stenting procedures.

Surgical revascularization

Patients over the age of 65 years account for more than 50% of coronary artery bypass grafting (CABG).[17] Surgical revascularization provides good symptomatic benefit but carries greater perioperative mortality in the elderly as a result of comorbidity. Indeed, the operative mortality rises from 5% in those over 70 years to nearly 9% in those over 80 years.[17] Predictors of worse outcome include poor left ventricular function, previous CABG, peripheral vascular disease, impaired renal function and diabetes mellitus. In patients who have multivessel disease in the presence of treated diabetes mellitus, CABG offered significantly better 5-year survival compared to PTCA.[40]

The risk of stroke is 2–10% and respiratory infections and renal impairment are also potential complications in the elderly. Despite these drawbacks, up to 95% of elderly patients are free from angina at 2 years post-CABG and 85% can participate in moderate physical activity.[41] In addition, an elderly patient who survives the operation without complication will have a 5-year mortality rate similar to an age-matched control.[17] The decision of suitability for surgical revascularization must therefore weigh up the immediate risk or mortality and morbidity with the longer term benefits and should be reached with active patient participation.

Stable angina

There are many patients in their 80s who provide a history of angina for 20 years without ever having undergone a definitive diagnostic investigation. They have often simply 'slowed down' to avoid precipitating an attack of angina. Providing treatment for these patients is based on the same principles as for younger patients, but there should be a greater awareness for potential adverse effects such as postural hypotension, negative inotropism, and peripheral edema. In the treatments of chronic stable angina, maximum anginal symptom relief should be achieved with mono- or dual therapy, because there is no evidence that triple therapy is advantageous. As discussed above, elderly patients with persistent angina who are on maximal medical therapy should be considered for revascularization with either PTCA or CABG.

Beta-blockers

Beta-blockers confer symptomatic and prognostic benefit. Evidence is based on high doses (e.g. atenolol 100 mg daily). In elderly practice, a lower starting dose is used owing to the increased frequency of symptomatic bradycardia and negative inotropism. Cardioselective agents (atenolol, bisoprolol, metoprolol) help avoid problems associated with the more prevalent airflow limitation disease in this group.

Nitrate therapy

Nitrate therapy for angina is convenient as monotherapy, preferably with spray preparations, without evidence of prognostic benefit. Nitrate-induced syncope is more common, especially with alcohol usage. Nitrates are contraindicated with sildenafil. This may limit their use in elderly men with co-existent CAD and impotency who have an increasing demand for restoration of erectile function.

Calcium channel blockers

Dihydropyridine calcium channel blockers, such as amlodipine, felodipine and nifedipine,

can be conveniently used as monotherapy in elderly patients with stable angina, particularly where hypertension co-exists. Indeed, a mortality benefit was seen in hypertensives over 60 years of age with nitrendipine, a long-acting dihydropyridine calcium antagonist.[42] In unstable angina, a meta-analysis detected no benefit of these agents in terms of mortality or morbidity, with a suggestion of an adverse effect in some studies.[43] The benzothiazepines (diltiazem) and phenylalkylamines (verapamil) have a greater action on the atrioventricular (AV) node with less peripheral vasodilation. There is evidence for a protective role for both diltiazem and verapamil in non-ST segment elevation AMI.[44] Postural hypotension occasionally occurs with the dihydropyridines but the commonest adverse effect is diuretic resistant edema. The combined negative inotropic effect of diltiazem or verapamil in combination with a beta-blocker may precipitate cardiac failure in elderly patients.

Potassium channel activators

Potassium channel activators, such as nicorandil, are thought to relieve angina by a mechanism that involves pre-conditioning of the myocardium in addition to nitrate-like actions. They are used widely in younger groups but there are no data in the elderly. A large randomized, placebo controlled trial of nicorandil as add-on therapy in chronic stable angina will be reporting in the near future.

Secondary prevention

Cardiovascular risk factor modification is paramount in all patients with documented CAD but is particularly important in the elderly who carry the higher mortality risk. Lifestyle modifications are important in order to limit the course of major cardiovascular pathologies, such as obstructive CAD and hypertension (Table 13.5). It is never too late for change. Some patients discover that retirement produces the very emphasis for healthy living that physicians should encourage. Hypertension, as will be discussed in a later section, should be aggressively treated, especially where isolated systolic hypertension exists. Elderly patients should also be screened for impaired glucose tolerance or frank diabetes mellitus.

Aiming to reduce blood pressure

- Weight reduction
- Salt restriction
- Alcohol consumption reduced to 2 units per day
- Low intensity physical exercise
- Increased fresh fruit and vegetable consumption

Aiming to reduce cardiovascular risk

- Cessation of smoking
- Reduced saturated fats
- Increased oily fish intake

Table 13.5
Lifestyle recommendations.

Dyslipidemia

The treatment of elevated blood lipids in patients without established cardiovascular disease is well established in the younger patient.[45] Five years of treatment substantially reduced cardiac mortality in men aged 45–64 years. The decision to commence lipid-lowering therapy in primary prevention is based on a specified threshold of coronary risk rather than on an absolute threshold lipid value.[46]

Patients over 70 without cardiovascular morbidity need not be screened. Total cholesterol in the elderly may be a poorer predictor of subsequent coronary events since plasma concentrations can be influenced by comorbidity.

In trials of lipid lowering for secondary prevention, older patients have also been included. Sub-analysis of the Scandinavian Simvastatin Survival Study (4S), which investigated patients with baseline total cholesterol 5.5–8.0 mmol/l, revealed highly significant 34% reduction for all-cause mortality, attributable to a 43% reduction in risk for coronary heart disease mortality in the 23% of patients over 65 years.[47] Five years of statin therapy was thus equivalent to the mortality reduction seen in younger patients. Similarly, retrospective analysis of the Cardiovascular and Recurrent Events (CARE) trial identified 1283 patients who were aged 65–75 years (average age 69 years) post-AMI, with plasma total cholesterol less than 6.2 mmol/l and average LDL of 3.57 mmol/l.[48] Treatment with pravastatin 40 mg for an average of 5 years produced a relative risk reduction of 32% for major coronary events, 45% for coronary death and 40% for stroke. It was calculated that only four older patients would need to be treated with pravastatin to prevent one cardiovascular event. This enhanced benefit to the elderly group results from the overall increase in mortality with age. The proposed upper age limit for beginning treatment in this context is 75 years.[47,48]

However, these analyses are limited by nonstratified randomization of the elderly patients to treatment or placebo arms and the small number of elderly women enrolled. To address these issues, a prospective trial of pravasatin is being undertaken in 5804 elderly patients with evidence of risk factors for vascular disease and who have a total cholesterol between 4.0–9.0 mmol/l.[49] Patients are aged 70–82 years, with more than 50% women. The primary outcome measure is the combined endpoint of CAD death, definite plus suspected AMI and fatal plus nonfatal stroke. A secondary endpoint will be an assessment of the ability of pravastatin to slow cognitive decline.

Hormone replacement therapy

The incidence of CAD in women rises significantly after the menopause. The potential cardioprotective benefits of hormone replacement therapy (HRT) remain controversial. There is substantial observational data which suggests lower rates of CAD in women taking HRT in the setting of primary prevention.[50] In secondary prevention, the Heart and Estrogen/progestin Replacement Study (HERS), the largest prospective placebo controlled clinical trial of HRT (0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate), failed to show the expected benefits.[51] There was an early trend of increased mortality in the treatment group attributed to an increase in thromboembolic events: this disappeared over the subsequent 4–5 years of the study, which was explained by the beneficial effects of HRT on plasma lipids. Indeed, LDL cholesterol was reduced by 11% with a rise in HDL cholesterol of 10%.

The inability to demonstrate an advantage of HRT in HERS may have resulted from several factors. The relatively short follow-up, the higher cardiovascular risk population compared to observational studies and the underuse of proven pharmacologic strategies, such as statins, beta-blockers and ACE inhibitors, in secondary prevention may all have contributed. Since HRT has noncardiovascular

benefits on bone density and vasomotor symptom relief, it remains an important therapy and should be considered in most postmenopausal females on an individual patient basis where the benefit-to-risk ratio is evaluated. It is not currently recommended for the prevention or treatment of CAD but can be used as a second-line lipid lowering agent. A large number of ongoing studies will further address the issue of cardiovascular protection with HRT.

Cardiac rehabilitation

Elderly patients with established CAD and normal cognitive function should be offered cardiac rehabilitation in order to maintain peak physical function and personal independence. Typical programs may have to be modified to allow for comorbidity. Physical endurance and functional capacity in older people can be improved by exercise training after an AMI.

Cardiac failure

Epidemiology

Congestive cardiac failure is common amongst patients over 65 years (Table 13.6): in this population, it affects up to 10% and is responsible for the largest number of acute admissions to hospital.[52] In patients hospitalized with heart failure, 78% are over 65 years and 50% are over 75 years.[6] In the community, only 17% of people with heart failure are less than 65 years of age.[53]

In the elderly, diastolic dysfunction is often the more common type of hemodynamic compromise since this phenomenon, as discussed, arises in part through the aging process. Indeed, as many as 70% of those aged over 80 with clinically defined cardiac failure have preserved left ventricular systolic function which contrasts with only 10% of patients below 60 years with similar clinical findings.[54] However, many elderly patients with diastolic dysfunction have underlying obstructive CAD or hypertension and may present acutely with congestive cardiac failure caused by ischemia or uncontrolled arterial blood pressures.[55]

Despite being more prevalent in the elderly, the majority of large randomized trials for heart failure treatment have focused on those aged below 65. In addition, there are no controlled trials of treatment of diastolic cardiac failure. The exclusion of the elderly from many studies and the lack of data on the management of diastolic dysfunction forces physicians either to extrapolate data to fit patients aged over 65 or to treat them empirically on the basis of symptoms. Prompt diagnosis and treatment of systolic dysfunction are essential in view of a 5-year mortality around 50% for

- Cardiac failure is common in the elderly
- Diastolic dysfunction is more common than systolic failure
- Diuretic therapy, particularly loop diuretics, offer good symptom relief
- Spironolactone, ACE inhibitors and beta-blockers have evidence of mortality reducing benefits from randomized trials in systolic failure
- There is less evidence for angiotensin II receptor antagonists, digoxin and the treatment of diastolic dysfunction

Table 13.6
Cardiac failure and aging.

mild disease and almost 100% for severe dysfunction with 1 year rates as much as 30%. The prognosis for diastolic dysfunction is better, but since this can progress to systolic dysfunction, it must also be detected early.

Clinical presentation

Cardiac failure in the elderly may present with the classic symptoms of exertional dyspnea, orthopnea and paroxysmal nocturnal dyspnea, but non-cardiac symptoms are also common. These include weakness, fatigue, anorexia, weight loss, confusion, depression and immobility. There are various precipitants to an acute episode of cardiac failure including tachy- and bradyarrhythmias, notably atrial fibrillation and sick sinus syndrome. Comorbidity such as anemia, chronic obstructive pulmonary disease, thyroid dysfunction or renal disease can all further impair an already reduced cardiac reserve.

Iatrogenic precipitation of cardiac failure in the elderly is all too common. In the community this can arise from co-prescription of non-steroidal anti-inflammatory drugs which impair sodium and water excretion and can antagonize ACE inhibitors, or corticosteroids which also lead to fluid retention. In the hospital setting, inattention to fluid balance, particularly in the perioperative period, may lead to excessive parental fluids and/or inadequate diuresis. Medications prescribed to treat cardiac symptoms can inadvertently cause acute deterioration of cardiac performance, either in therapeutic doses, e.g. calcium antagonists, beta-blockers and anti-arrythymics or in toxicity, e.g. digoxin.

Investigations

The clinical distinction between diastolic and systolic heart failure is difficult. There may be a combination of both in some patients, especially in the later stages of the disease. The most useful diagnostic tool in this context is echocardiography as there are now clear guidelines for the positive diagnosis of diastolic dysfunction in heart failure.[56] An echocardiogram may also detect valve pathology or unexpected pericardial effusions and although it should be available to all older patients with symptoms of cardiac failure, it must follow a good clinical examination and simple investigations. In the presence of a normal 12-lead ECG and normal chest X-ray, significant impairment of left ventricular function is unusual and an echocardiogram is generally not required.

Management

Systolic heart failure management in elderly patients requires the use of diuretics, ACE inhibitors, other vasodilators, beta-adrenoceptor blockers, digoxin and oxygen supplementation. Thus, before even taking into account co-morbidity, anti-failure polypharmacy is a problem that may rapidly develop.

Diuretics

Non-potassium sparing diuretics, which act by reducing venous return, lowering ventricular filling pressures and increasing body fluid loss, offer excellent symptomatic relief, but there is no prognostic benefit associated with their use. Treatment with thiazide diuretics is limited by the glomerular filtration rate (GFR) which, as discussed, declines with age. They become ineffective when the GFR is less than

30–40 ml/min. Loop diuretics such as frusemide are preferred. The more potent agents, such as metolazone, should be reserved for resistant fluid retention with meticulous electrolyte monitoring required.

The use of potassium sparing diuretics in the elderly is problematic. Despite an age-related reduction in total body potassium content, associated with reduced lean body mass, plasma potassium concentration remains unaltered.[57] There is thus a danger of potassium retention and hyperkalemia, particularly with the combined use of ACE inhibitors.

The aldosterone antagonist spironolactone 25 mg given daily in addition to loop diuretic, ACE inhibitor and digoxin was shown in the Randomised Aldactone Evaluation Study (RALES) to reduce mortality from progressive cardiac failure and sudden cardiac death by 30% in patients with New York Heart Association (NYHA) class III and IV heart failure.[58] There was also a 35% reduction in hospitalization for worsening heart failure.

The mean age of patients in the study was 65 years with mean follow-up of 2 years. The mean doses of ACE inhibitors used here were relatively low in comparison to the ACE inhibitor trials, which may have explained some of the benefits observed since spironolactone was acting on an inadequately suppressed renin-angiotension system. Thus, although spironolactone has prognostic benefit in the patients entering the elderly 'phase' of life, routine use would probably not be recommended in those who are older because of the risk of hyperkalemia, as with other potassium sparing diuretics. The case for spironolactone would be stronger if an ACE inhibitor was not tolerated.

With all diuretics, in addition to the metabolic effects of hyponatremia, uremia and uricemia there is a risk of over-dieresis if the dose at commencement is too high. If the patient has mobility problems, incontinence can result and urinary retention is an additional risk. To avoid these problems, diuretics should be commenced in small doses and titrated upwards according to response.

ACE inhibitors

ACE inhibitors are undoubtedly beneficial for patients with cardiac failure, both at improving hemodynamics and reducing mortality. A meta-analysis of the results from all of the major trials reports a reduction of 23% in total mortality and 35% for the composite endpoint of total mortality and heart failure-related hospitalization.[59] Although none of these trials were specifically targeted at the elderly population, the upper age limit was either 80 years[60,61] or there was no upper age limit.[62] The average age in the Co-operative North Scandinavian Enalapril Survival Study (CONSENSUS), one of the first to complete, was 70 years with results showing a 40% 6-month and 31% 1-year reduction in mortality.[63]

ACE inhibitors should therefore be prescribed to all patients with evidence of left ventricular systolic function. Recent evidence from the Heart Outcomes Prevention Evaluation (HOPE) trial suggests that ACE inhibition offers a generalized 'vascular protective' effect which can be achieved in practice even in the absence of left ventricular systolic dysfunction.[64] Ramipril was compared with placebo in patients of mean age 66 years who had one historical risk factor of either ischemic heart disease, peripheral vascular disease, cerebrovascular disease, or diabetes and at least one cardiovascular risk factor

(hypertension, dyslipidemia, smoking or microalbuminuria). Left ventricular function was impaired (LVEF $< 40\%$) in only 2.6% of the study population. Ramipril reduced the composite endpoint of AMI, stroke and death from cardiovascular causes by 22% without any major effect on blood pressure reduction. Fewer patients in the ACE inhibitor arm went on to develop heart failure and the results were, if anything, better in the elderly compared to those under 65 years.

However, despite the few absolute contraindications to ACE inhibitors, the elderly population often escape treatment as discussed in the setting of post-AMI or are maintained on an inadequate dose. This may occur because of fears of first-dose hypotension or of the effects on renal function caused by concomitant renovascular disease. In reality, first-dose hypotension is rarely a problem with the modern agents and can be avoided by ensuring that patients are not intravascularly volume-depleted, e.g. by missing a dose of diuretic. The elderly do have generalized atherosclerosis which may increase the risk of renal artery stenosis. Renal function should therefore be monitored closely and ACE inhibitor discontinued only if serum creatinine is persistently raised. In terms of selecting dose, evidence suggests that high-dose ACE inhibition is more beneficial than low-dose and consequently the maximum tolerated dose should be used.[65]

Cough, which may be confused with paroxysmal nocturnal dyspnea, is a significant adverse effect of ACE inhibitors which is particularly common in the elderly. It is thought to result from enhanced bradykinin bioavailability as a result of simultaneous kininase II inhibition. This mechanism may also account for some of the benefits with ACE inhibitors and, there is evidence to suggest that approximately 20% of the blood pressure response to ACE inhibitors is mediated through bradykinin B_2 receptors.[66]

Angiotensin II receptor antagonists

Angiotensin II receptor antagonists are generally better tolerated than ACE inhibitors. They do not inhibit bradykinin breakdown and therefore do not cause cough. However, angiotensin II receptor antagonists have not proved to be superior in reducing mortality compared to ACE inhibitors in prospective randomized control trials of patients with heart failure, perhaps in part as a result of different effects on bradykinin. The Evaluation of Losartan in the Elderly study (ELITE I) compared an angiotensin II type 1 receptor antagonist with an ACE inhibitor in 722 patients aged over 65 who had symptomatic cardiac failure and left-ventricular dysfunction.[67] Losartan therapy was associated with a reduction in all-cause mortality, although a secondary endpoint finding, compared to captopril, but the number of deaths was small. However, in the larger follow-up study of over 3000 patients in ELITE II, which was powered only to show superiority of losartan over captopril, there were no significant differences in cardiovascular events between the treatment groups but fewer side-effects in the losartan arm.[28] It was concluded that the better tolerated angiotensin II receptor antagonists should be reserved for patients intolerant of ACE inhibitors in patients with heart failure.

The Valsartan Heart Failure Trial (Val HeFT), where the average age was approximately 62 years, reported at the 73rd American Heart Association annual conference, November 2000.[68] This study investigated the potential benefits of a combination of valsartan and captopril versus placebo and

captopril. There was a combined primary endpoint of all-cause mortality or mortality and morbidity where morbidity included congestive cardiac failure hospitalization, resuscitated sudden death and administration of intravenous inotropes or vasodilators for more than 4 hours. The theoretical concept was that combination therapy would inhibit angiotensin II synthesis and receptor binding with the additional benefits of increased bradykinin bioavailability. There was no significant difference in all-cause mortality, but there was a relative risk reduction of 13% for the mortality/morbidity endpoint (mainly because of a 27% reduction in CCF hospitalization) in the combination arm. However, subgroup analysis of the combination arm revealed that the minority of patients not on ACE inhibitors (7%) had a greater benefit than patients on ACE inhibitors, whilst those patients on beta-blockers had worse outcome than those not taking beta-blockers. Further large randomized studies with angiotensin II receptor antagonists are ongoing and will be required to support or refute the use of these drugs in heart failure.

Beta-blockers

Despite trial results from the 1970s that favored the use of beta-adrenoceptor blockers in cardiac failure, it was not until 1996 that the results from the first prospective randomised controlled trial became available.[69] Since then, there have been several large studies with bisoprolol,[70] metoprolol[71] or carvedilol[72] which looked at NYHA class II, III and IV cardiac failure patients and resulted in a remarkably similar mortality risk reduction of approximately 35%. Although not looking specifically at elderly patients, the upper age limit of the combined 10 021 subjects was 80–85 years, with a range of mean ages across the trials of 58–64 years. In the MERIT-HF study with metoprolol, almost a third of patients randomized were over 70 years of age.[71] Thus, the evidence for using beta-blockers for cardiac failure in patients aged 60–70 years is clear, and even in older patients, beta-blockers should be considered, particularly when there is a history of ischemic heart disease. One study of beta-blockers in heart failure which did not report mortality benefit was the Beta-blocker Evaluation Survival Trial (BEST) with bucindolol in NYHA class III and IV patients.[73] It may have been that the presence of intrinsic sympathomimetic activity with this agent limited its potential benefit in these patients.

Digoxin

The role of digoxin in normal sinus rhythm and cardiac failure has been debated for many years. Data shows no reduction in overall mortality but a reduced rate of hospitalization and overall improvement in quality of life without significant toxicity.[74] Maximum benefit was for patients with LVEF $<25\%$, non-ischemic heart failure of NYHA class III or IV. Practice suggests that patients with significant failure already on digoxin should continue, but it should not be initiated as first-line therapy, unless patients have a very low ejection fraction or are refractory to other treatments. Regular monitoring for toxicity should be performed, especially in those patients with impaired renal function, because of the narrow therapeutic window.[75]

Vasodilators

There is evidence for the combined use of hydralazine and isosorbide mononitrate in cardiac failure to improve mortality. In prac-

tice, the use of these agents together has been superseded by the other therapies above. They can be used however for patients who are intolerant of ACE inhibitors.[76]

Anticoagulation

Initial subgroup analysis of the major ACE inhibitor trials suggested that those patients who were taking aspirin in addition to ACE inhibitor had less benefit in terms of a reduction in cardiovascular events than patients not on aspirin. However, a systematic overview of individual data from 96 712 randomized patients who took ACE inhibitors post-AMI demonstrated similar proportional reductions in 30-day mortality among the patients taking concomitant aspirin therapy (89%) and among patients not taking aspirin.[77]

Whether aspirin is the most suitable agent to prevent thromboembolic disease in severe cardiac failure is also debated. The Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial is a large randomized study which aims to determine the most suitable antithrombotic agent in chronic heart failure and evaluate the potentially harmful interaction of aspirin and ACE inhibitors in cardiac failure prospectively. Open-labelled warfarin is compared against aspirin or clopidogrel which is double-blinded. Patients with LVEF $<35\%$ are currently being recruited and the study is currently expected to report in 2004.

The risk of thromboembolic events, including deep vein thrombosis, may be relatively high in the elderly immobile patient with severe left ventricular failure, especially when there is co-existing atrial fibrillation. These patients should probably be anticoagulated with warfarin until mobility is improved.[78] Physical activity should also be encouraged.

Non-pharmacologic measures

In addition to drug therapy, lifestyle changes are as appropriate to the elderly patient as they are to their younger counterparts (see Table 13.5). Pharmacologic therapy can suffer from poor compliance, particularly with diuretics and when patients have so many drugs to remember. Advice on salt restriction is important, although this is impeded by the high salt content of 'ready meals' on which many elderly people rely. Fluid restriction is potentially dangerous and should probably be avoided. Daily weight assessment can be useful and may allow gentle titration of diuretic dose by the patients themselves. Cardiac cachexia can occur by a mechanism that remains unresolved.

When assessing an elderly patient with cardiac failure it is essential to consider the effect that the disease will have on their everyday life. Restoration of independence is important and can be achieved for example with home improvements such as stair lifts. Providing regular assistance in the home, such as home helps and ready-cooked meals delivered to the door and other vital services, aids the patient's rehabilitation at home. In the UK, nurse-led 'mobile' heart failure clinics have been developed where patients are seen in their own home. Trained nurses deliver and adjust medications and spend more time with the patient than is otherwise possible in the conventional hospital setting. This looks set to become a valuable management strategy.[79]

Heart failure secondary to diastolic dysfunction

Aside from a more favorable prognosis, diastolic dysfunction requires a different therapeutic approach. The most important goal is to restore ventricular relaxation and consequently

filling. Obvious precipitants of diastolic dysfunction, such as hypertension and anemia, should be avoided. In addition, low dose diuretics can be useful, although at higher doses intravascular volume depletion may occur lowering preload and exacerbating symptoms. Calcium channel antagonists may have a beneficial effect on diastolic function in patients with coronary disease or hypertension and there are ongoing studies with ACE inhibitors.[80]

Atrial fibrillation

The prevalence of atrial fibrillation rises sharply from 0.5% in those aged 50–59 years to 8.8% in those aged 80–89 years (Table 13.7).[81] Atrial fibrillation is an important cause of embolic phenomena and increases the risk of a cerebrovascular accident, which may effect up to 30% of those aged 80–89 years, compared with 1.5% of 50–59 year olds. In addition to morbidity, atrial fibrillation is associated with a 1.5–1.9 fold mortality risk after adjustment for pre-existing cardiovascular conditions.[82]

Seventy per cent of all cases of chronic atrial fibrillation have significant underlying cardiac pathology. The patient has 'lone atrial fibrillation' in the absence of cardiac disease. Chronic atrial fibrillation can be paroxysmal atrial fibrillation, persistent or permanent. The clinical impact of paroxysms increases with their severity and frequency and when they occur continuously the term 'persistent' is preferred. Permanent atrial fibrillation implies resistance to previous cardioversion and an inability to return to sinus rhythm. Primarily these patients require ventricular rate control in contrast to paroxysmal or persistent atrial fibrillation where the therapeutic goal is restoration and maintenance of sinus rhythm.[83]

- The prevalence of atrial fibrillation increases with age
- Loss of co-ordinated atrial systole can precipitate pulmonary and systemic congestion, even with normal left ventricular systolic function
- Ventricular rate control, suitability for cardioversion and overall risk of thromboembolic phenomena should be addressed early
- Echocardiography is the best means to assess thromboembolic risk in those aged 65–74 with no evident clinical risk factors
- Digoxin can be used alone for rate control in permanent atrial fibrillation, but beta-blockers or rate-limiting calcium antagonists should be used with digoxin for patients with exercise-exacerbated atrial fibrillation or paroxysmal atrial fibrillation

Table 13.7
Atrial fibrillation and aging.

Management

Ventricular rate maintained at 60–80 beats per minute (bpm) resting and 90–115 bpm during exercise will improve ventricular function, help avoid tachycardiomyopathy and perhaps reduce the risk of ventricular arrhythmias. The risk of thromboembolism will probably remain the same. Rate control is best achieved with digoxin combined with beta-blockers or rate-limiting calcium channel antagonists (diltiazem and verapamil) since digoxin alone is often ineffective during exercise. Digoxin alone is also best avoided in paroxysmal atrial fibrillation as it can increase frequency and

severity of attacks. Amiodarone can be effective but has serious adverse effects with longterm use.

All newly diagnosed cases of atrial fibrillation should be considered early for cardioversion, since atrial fibrillation rapidly induces atrial remodelling which in turn leads to persistent morphological changes and reduces the chance of longterm success. A poor chance of maintaining sinus rhythm once established or a high complication risk during the procedure argues against cardioversion. However, restoration of sinus rhythm may relieve symptoms, improve exercise tolerance, avoid the need for medication and perhaps lower the risk of thromboembolic disease.[83]

Sustained atrial fibrillation (>48 hours) requires warfarin, with an international normalized ratio (INR) 2.0–3.0, for at least 3 weeks prior to cardioversion and then 4 weeks afterwards because of atrial 'stunning'. Pharmacologic cardioversion is generally only effective for atrial fibrillation of recent onset. External electrical cardioversion under general anesthesia, to deliver an R wave synchronized shock of 200 J, is the preferred choice having a success rate of 65–90%.[83]

Non-rheumatic atrial fibrillation carries a 5.6 fold increase in embolic risk which rises to 17.6 fold when associated with rheumatic valve disease.[84] Clinical and echocardiographic variables significantly alter the thromboembolic risk in atrial fibrillation (Table 13.8). Cardiovascular disease and advancing age in the presence of other risk factors have a major role in risk stratification (Table 13.9). A patient over 75 years even with frequent paroxysmal atrial fibrillation and structural cardiac disease, has a relatively high risk of a thromboembolic event.[85]

The major trials demonstrated an average embolic relative risk reduction of 68% using warfarin with an INR 1.5–4.5 in patients with atrial fibrillation.[86] More hemorrhagic events were associated with warfarin particularly in the presence of uncontrolled hypertension and INRs greater than 3.0. The European Task force therefore recommends individual risk-benefit ratio assessment with introduction of warfarin to achieve an INR of 2.0–3.0 in high

Clinical risks	*Echocardiographic risks*
Previous embolic or cerebrovascular event	Significant valve disease
Obstructive coronary artery disease	Left atrial thrombus
Congestive cardiac failure	Left ventricular dysfunction
Hypertension	Left atrial size >50 mm
Diabetes mellitus	Left atrial mechanical dysfunction

Table 13.8
Predisposing factors in the elderly patient for stroke in atrial fibrillation.

Risk	*Criteria*
High (12% annually)	• Previous embolic or cerebrovascular event • Significant valve disease or left ventricular dysfunction • Left atrial thrombus • Age >75 years with other clinical or echocardiographic risks
Moderate (8% annually)	• Age 65–74 years • Age <65 years with other clinical or echocardiographic risks
Low (1% annually)	• Age <65 years with no other clinical or echocardiographic risks

Table 13.9
Thromboembolic risk stratification in atrial fibrillation in the elderly patient.

risk individuals who warrant anticoagulation.[83] The US has similar guidelines.

Anticoagulation with warfarin may be dangerous in patients with cognitive impairment (that affects compliance), recurrent falls, and recent history of gastrointestinal bleeding. Aspirin, alone or in combination with low dose warfarin (INR < 1.5) was less effective in stroke reduction amongst high-risk patients but is more convenient and theoretically safer. Unless warfarin is contraindicated, aspirin is best reserved for medium or low-risk atrial fibrillation patients. The optimum dose is not clear, with 75–325 mg used in studies: the authors currently recommended 75 mg daily.

Atrial fibrillation refractory to medical treatment may require electrophysiologic studies to map accessory pathways and destroy them with radiofrequency ablation. Biatrial synchronous pacing may suppress atrial re-entrant tachycardias: implantable atrial defibrillators that deliver low-energy (<6 J) shocks are under clinical evaluation.

Hypertension

Systolic and diastolic blood pressure rise almost linearly as we grow older until approximately 65 years of age, when diastolic pressure begins to fall while systolic pressure continues to rise (Table 13.10).[87] Isolated sys-

- Isolated systolic hypertension is most common in elderly patients
- Evidence exists for the benefit of treating isolated systolic hypertension up to 85 years
- Most anti-hypertensive therapies have similar efficacy and individual drug choice may depend on a variety of factors, including comorbidity
- Thiazide diuretics and calcium channel antagonists reduce blood pressure in elderly hypertensives

Table 13.10
Hypertension and aging.

tolic hypertension (ISH) is a condition almost exclusive to the elderly population and, by the age of 85, more than 50% will be affected.[87] Hypertension, and particularly ISH, is probably the major cardiovascular risk factor for stroke, cardiac failure, CAD, and peripheral vascular disease.[88] Evidence now supports the theory that pulse pressure may be the best predictor of adverse cardiovascular effects in the elderly because low diastolic pressure may be linked to higher mortality rates in this population.[89]

Management

There is significant prognostic benefit in treating ISH up to 80 years of age and maybe even up to 85 years in the presence of end-organ damage. Large clinical trials in the elderly have shown a reduction in cardiovascular events and cerebrovascular disease, with a reduction in systolic blood pressure.[90] Generally, the effect on stroke reduction is greater than that seen on coronary events.[89] Reducing systolic blood pressure below 140 mmHg in the elderly is associated with a 50% reduction in dementia.[42]

Most drugs that lower total peripheral resistance or arterial stiffness, will effectively reduce blood pressure and many have data from outcome trials which demonstrate that in lowering blood pressure, they also confer prognostic benefit.[89] Treating to target levels is always more difficult in practice compared to trials, but current recommendations are $<$140/90 mmHg in the non-diabetic and $<$130/80 mmHg in diabetic patients.[91]

The choice of drug is best achieved by tailoring the regime to the individual with awareness of synergistic combinations, since ISH is often drug-resistant and may require dual or triple therapy for adequate control. Overall efficacies of the major classes of antihypertensives are similar, although a greater reduction in blood pressure has been observed with thiazide diuretics and calcium channel antagonists in older hypertensives.[92] Thiazides should be used with caution in patients with gout, renal failure, diabetes mellitus and dyslipidemia. Calcium channel antagonists are useful in patients with ISH or coexisting angina but cautioned in cardiac failure. ACE inhibitors are of value in hypertensives with diabetic nephropathy or cardiac failure. Nocturnal dosing without a diuretic, minimizes first dose postural hypotension.

Summary

Cardiovascular diseases in elderly patients are common and are a cause of significant morbidity and mortality in this population. The distinction between physiologic and pathologic changes in structure and function of the cardiovascular system has often been difficult but is now aided by the use of more sophisticated investigative techniques. It is important that, once recognized, common cardiovascular diseases are treated appropriately, as the benefits of treatment are usually at least as good as those obtained with younger patients and often these benefits are greater. The evidence base for much of the pharmacologic management of cardiovascular disease is based on data obtained from younger patients. In elderly care, best medical practice usually requires appropriate extrapolation of this data, together with good prescribing habits with special attention to co-existing morbidity, both biologic and social.

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14

Laser Myocardial Revascularization

Richard J Allen and Simon R Redwood

Introduction

Advances in the conventional methods of revascularization, coronary artery bypass surgery and percutaneous angioplasty, have led to the successful treatment of increasing numbers of patients with coronary artery disease. However, there remains a sizeable proportion of patients with severe coronary disease who are unsuitable for these procedures and who remain very symptomatic despite optimal medication. These patients take up large amounts of medical resources and often require repeated hospital admissions and regular outpatient follow-up.

Patients who are unsuitable for bypass surgery or angioplasty tend to fall into two main categories. There are those who have had previous operations and percutaneous procedures and in whom repeat coronary intervention is deemed too high risk and/or unlikely to be successful. The second group are those with diffuse coronary disease, often diabetic or elderly, who are known to do badly with these conventional treatments. The prolonged survival of coronary patients and the increasingly aged patient population means that the proportion of coronary patients in these two groups is growing and increasingly becoming a difficult clinical problem. The search for alternative methods of myocardial revascularization has led to the treatment strategy of direct myocardial perfusion through laser channels, termed 'laser myocardial revascularization' (TMLR).

Historical perspective

The original hypothesis of direct myocardial perfusion dates back to the 1930s when Wearn[1] first demonstrated the existence of direct communications between the heart chambers and the myocardial sinusoids. He suggested the possibility that, in the presence of coronary artery disease, the myocardium could be supplied directly from the left ventricle.[1,2] The model was based on observation of reptilian myocardial anatomy. It was noted that, in reptiles, the external coronary vessels are very small in comparison with the size of the heart. Histologic sections (Fig. 14.1) show the reptile myocardium to be divided into two distinct zones. The coronary vessels supply a thin periphery, consisting of about one twelfth of the reptile myocardial mass. The main bulk of the reptile myocardium is supplied by partially oxygenated blood directly from the left ventricular cavity via a sinusoidal subendocardial network. In normal adult human hearts the arterioluminal sinusoids are poorly developed.[3] By creating a series of channels between the ventricular cavity and the

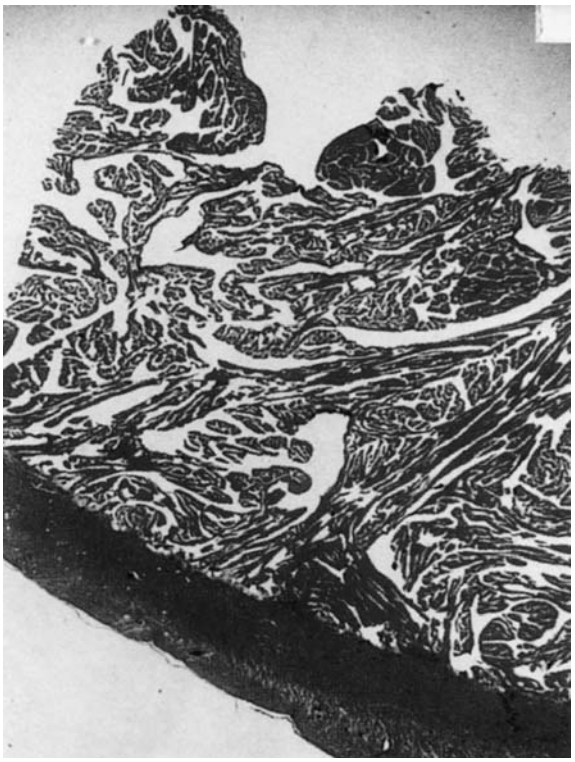

Figure 14.1
Trichrome-stained histological section of alligator heart (× 1.5). Spanning the entire left ventricular wall, the spongy endocardium with extensive channels and sinusoids can be seen, as can the densely epicardial region.

myocardium in the human heart, it was proposed that this might improve the myocardial perfusion.

This concept of direct myocardial perfusion subsequently led to many attempts at realization. From the 1930s, Beck tried a series of operations, which included omentopexy and myopexy procedures, in an attempt to establish a collateral circulation and to take advantage of myocardial neocapillary formation.[4,5]

In the 1950s, Vineberg[7] pioneered several revascularization operations, most notably the implantation of internal mammary artery implants directly into left ventricular myocardium.[6] He found that, despite connecting a high pressure and flow vessel directly into the myocardium, virtually no hematoma formation was seen, which suggested that the myocardial capillary network was extensive enough to soak up the arterial blood. At about the same time, other experimental techniques were also tried by a number of surgeons with mixed results.[7–9]

The work carried out by Sen and colleagues in the 1960s is of particular relevance.[10] He performed myocardial acupuncture on dogs by passing thin needles directly through the myocardium into the left ventricular cavity. A series of operations, involving ligature of the left anterior descending artery (LAD), suggested improved perfusion of 'treated' myocardium against controls with protection against infarction and improved survival. Histologic analysis of the channels suggested that they remained patent and contained red blood cells up to 8 weeks later.

Limited success and the advent of coronary artery bypass surgery led to a decline in interest in direct revascularization procedures. Furthermore, Pifarre et al reported their findings in 1969 which suggested that passive diffusion from the left ventricle was physiologically unlikely.[11,12] They took simultaneous pressure recordings, in canine hearts, of the left ventricle, aorta and intramural segments of myocardium that had been implanted by venous grafts. They found that, during systole, the intramural pressure was greater than in the left ventricular cavity and aorta by as much as 50–100 mmHg. During diastole, the intramural pressure was 20–70 mmHg lower than in the aorta, but at all times greater than in the

ventricle (an average of 20 mmHg higher). These findings confirmed that coronary blood flow and perfusion of myocardium occurs during diastole. The investigators also concluded that there was no possibility at any time during the cardiac cycle, systole or diastole, for blood to flow from the ventricle to the myocardium.

The emergence of TMLR

The re-emergence of the concept of direct myocardial revascularization occurred in the early 1980s. Mirhoseini pioneered early animal experiments that involved the use of a CO_2 laser.[13,14] The development of lasers was thought to provide several potential advantages over mechanical means. Firstly, channel formation is quick and clean. Cell damage to surrounding tissue is less and the tissue is removed by vaporization which results in little debris and minimal scarring. Preliminary studies of CO_2 lasers showed that they could be used on the beating heart and that laser energy could permeate from the epicardium to the endocardium with minimal damage to the surrounding tissue. Bleeding caused by creation of the channels was limited, and channel size could be altered according to wish (Fig. 14.2).

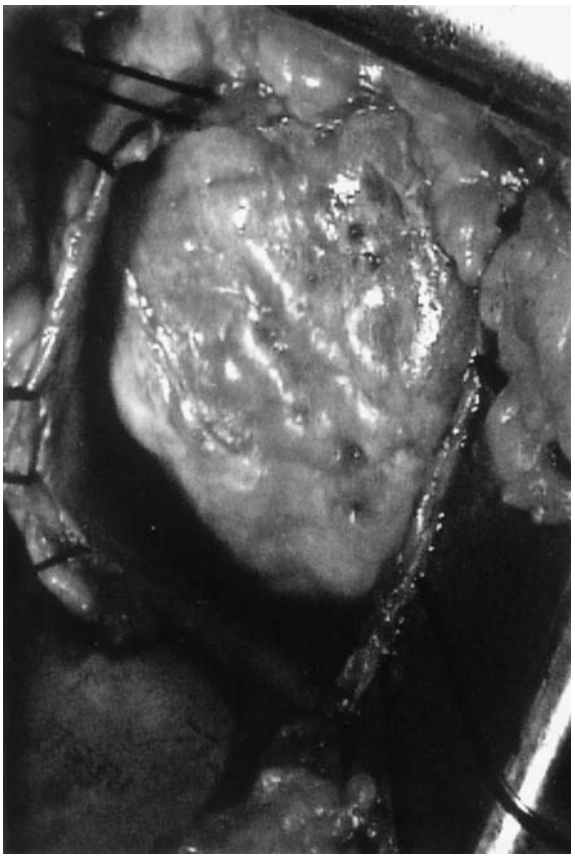

Figure 14.2
Laser channels, approximately 1 mm in diameter, spaced 1 cm apart across exposed left ventricle.

Mirhoseini et al published the results of an experiment involving 24 mongrel dogs.[15] The dogs were divided into four groups of six each. Three of the groups underwent laser channel treatment to the LAD left ventricular area, using a high-powered 400W CO_2 laser, with differing amounts of the total LAD area treated. The fourth placebo group had no laser treatment. All dogs then underwent ligature closure of the proximal LAD. All dogs in the placebo group died within 20 minutes, despite vigorous attempts at resuscitation. In the group where a small area, 1 cm^2, underwent laser treatment, an acute survival of 33% occurred. The other 2 groups, both of which had extensive areas of laser treatment, had survivals of 83% and 100%. The survivors were sacrificed at various intervals later for autopsy. The epicardial component of the channel was clearly visible and penetration through the myocardium could be seen.

Histology revealed patent endothelial channels and viable surrounding myocardium. Areas not treated by laser had myocardial scarring. The findings suggested the treated areas were protected from infarction by means of an alternate blood supply through the channels.

Further animal studies tested the ability of laser channels to supply blood acutely to ischemic tissue.[16–18] All of these experiments involved coronary artery occlusion shortly after or shortly before laser channel creation, which suggested that the channels supply blood immediately to the ischemic tissue. Consistent improvements in mortality and preservation of contractile function were reported following laser treatment.

Laser devices

Three main laser types (carbon dioxide (CO_2), holmium:yttrium-aluminum-garnet (holmium:YAG) and excimer) have been used to create channels in TMLR. Depending on type, the lasers deliver different energy outputs, channel morphology and levels of surrounding tissue trauma. The relative merits of each type of laser are still not fully understood.

Carbon dioxide lasers

Carbon dioxide (CO_2) lasers were the original lasers used in early TMLR studies. They emit infrared radiation and generate high-powered continuous-wave energy, capable of delivering approximately 800 W of peak power to the tissue with maximal pulse energies of 80 J. The energy is absorbed by the water present in the tissues, which is heated to a super vibrational state. This vibrational energy is transferred to organic molecules, which are caused to vibrate to the extent that their molecular bonds break to create fragments so small that they dissipate as gases. Temperatures increase to 350–450° C and the myocardium is instantaneously vaporized, so producing a channel with a single burst of energy.

Holmium:YAG lasers

Holmium:YAG lasers also emit infrared radiation, however the power delivery is pulsed. The pulse duration is typically 250 μs. Laser channels are created using repeated bursts of energy. In the case of TMLR, an average of 3–10 bursts is required per channel (total energy 20–30 J per channel). Histology has shown that the size of the channel core and the area of thermally damaged tissue are larger with holmium:YAG lasers than with CO_2 lasers.[19] This would be expected because of the differing energy characteristics of the two laser beams. The channels however became largely indistinguishable at 6 weeks, with the channel cores occluded by thrombus.

Excimer laser

Excimer lasers produce pulses of lower powered energy at one wavelength (308 nm). The pulses can be adjusted for intensity per pulse of energy, ranging from 9 to 15 mJ, which determines the degree of tissue ablation. The speed of ablation is determined by the number of pulses per second, which can also be varied and ranges from 1 to 240 Hz. Typically, 200–300 pulses are required per channel. Excimer lasers are referred to as 'cold' lasers as they operate in the deep ultraviolet spectrum, in which the laser energy is not absorbed by water. Conversely, the excimer possesses much greater photon energy than the infrared lasers, adequate to cause

bond dissociation by direct photon collisions with organic molecular bonds. The deep ultraviolet output of the excimer is not absorbed by water, allowing it to remain cool and able to quench any heat energy released by the breakage of the ablated organic molecular bonds. This may minimize thermal injury to neighbouring tissues, although no direct comparisons have been reported. Mack et al compared the histology of channels formed by excimer laser with those formed by acupuncture.[20] The results suggested improved channel patency with laser-created channels and little in the way of surrounding inflammation.

TMLR studies

Mirhoseini performed the first human trials. In 1983, a patient underwent successful combined CABG and TMLR to an area of myocardium unsuitable for bypass grafting. In 1988, Mirhoseini et al published the results of laser revascularization on 12 patients.[21] These patients selected were candidates for bypass grafting with at least one vessel that could be bypassed, but in whom complete revascularization was not thought possible either because of diffuse small vessel disease or because of total occlusion of a vessel in myocardial territory considered viable. Patients underwent a combination of bypass grafting and laser channel revascularization using an 80 W CO_2 laser. The channels were created from the epicardial surface of the heart to the endocardium. The number of channels was determined by the size of the area treated, usually 10–12 channels. Results were impressive. Operative mortality was zero. Clinical improvement was noted in all patients. Improved perfusion on nuclear scintigraphy in the laser-treated areas was reported as well as improved left ventricular function. Patent channels were demonstrated by follow-up left ventriculography in 6 of 10 patients examined.

The first of the large multicenter trials was started in 1992 and involved eight centers in the United States. Horvath et al published the results in 1997.[22] TMLR was used as the sole therapy for patients with intractable angina who were deemed not amenable to the conventional methods of revascularization. Two hundred patients were enrolled over a 3-year period. At enrolment, all patients had Canadian Cardiovascular Society (CCS) class III or IV angina and evidence of reversible ischemia in one or more left ventricular territories. Laser channels were created using a 1000 W CO_2 device. An average of 30 ± 12 laser pulses was delivered in each procedure. Thirty-day perioperative mortality was 9%, with myocardial ischemia and heart failure listed as the most common causes. There was also a subsequent further 9% mortality at 1 year. However, significant improvements in angina class were reported at 3, 6 and 12 months ($p < 0.001$). Seventy-five percent of patients had a 2+ angina class reduction and a third of patients reported no angina throughout the average 10 ± 3 month follow up. There was a decrease in the number of perfusion defects detected on radionuclide scanning in the treated myocardial areas. There was also a significant decrease in the number of hospital admissions for angina in the year following TMLR.

The results of this study highlighted the great difficulties in properly assessing new methods of myocardial revascularization. The study did not have a randomized control group. Undergoing a new laser treatment and an operative procedure carry an obvious marked placebo effect, which was difficult to

quantify. The improvements in myocardial perfusion could also be criticized because of lack of controls. The high peri-operative and 1-year mortality results were also of concern.

Nagele et al published their results in 1998 from a single centre study carried out in Hamburg, Germany.[23] Again sole TMLR was carried out, using a CO_2 laser, on patients with intractable angina who were on optimal medical management and who were unsuitable for CABG or angioplasty. Sixty patients were treated and followed up for a mean period of 1.94 ± 0.8 years, significantly longer than in the US study. Perioperative 30-day mortality was 12% (7 patients). The mortality at 1 and 3 years was 23% and 30%, respectively. The main predictor of poor outcome was again pre-procedure poor left ventricular ejection fraction. Those patients with LVEF <40%, had significantly greater risk ($p < 0.001$) compared to all other groups. Significant early improvements in angina class were detected in the TMLR group with a mean reduction from 3.31 ± 0.51 to 1.81 ± 0.77 after 3 months. However, a gradual return in symptoms and worsening of angina class was reported after 6 months, and again at 1, 2 and 3 years. Myocardial perfusion scans showed a significant increase in non-viable myocardium ($p < 0.05$) and no significant change in ischemic segments.

In 1999, the first results of large randomized control trials were reported. Frazier et al from the Texas Heart Institute published the findings of a prospective, controlled, multicenter trial.[24] Twelve centers participated and, between 1995 and 1997, recruited 192 patients who had limiting angina and were unsuitable for CABG or PTCA. Subjects were randomized either to TMLR with CO_2 laser (91 patients) or to continued medical management (101 patients). However, 60 of those assigned to medical management were crossed-over to TMLR a mean of 107 days after randomization. Perioperative mortality following TMLR was 3%. Twelve-month survival rate was 85% in the TMLR group and only 79% in the medical management patients that had not crossed over. Median hospital stay was 7 days following TMLR. Thirty-eight percent of patients had at least one complication (acute MI 7%, congestive cardiac failure 11%, ventricular tachycardia/fibrillation 8%).

Symptomatic benefit of TMLR over medical management was marked. At 3 months, 67% of the TMLR group had 2+ CCS angina class improvement, significantly better than the medical management group (including those crossed over) ($p < 0.001$). The benefits were sustained at 12 months follow-up. Patients in the TMLR group also had significantly improved quality of life as measured by the SF36 and Seattle Angina questionnaires ($p < 0.001$).

Myocardial perfusion was measured by radionuclide SPECT scanning at enrolment, 3, 6, and 12 months. In the TMLR group, reversible ischemia decreased by an average of 1.5 segments per patient at 3 months, 0.8 segments at 6 months and 1.4 segments at 12 months. In comparison, the medical management group had evidence of an increased number of perfusion defects at all stages, which was significantly worse than the TMLR group ($p = 0.001$, 0.02, 0.002). The results of this study led to the Food and Drug Administration approving the technology and TMLR as a treatment for ischemic heart disease.[25]

The results of the ECLIPSE multicenter US trial were published at the same time by Allen et al.[26] Patients with similar entry criteria and CCS class IV angina were randomized either

to TMLR using a holmium:YAG laser or to continued medical therapy. Eighteen centers recruited a total of 275 patients between March 1996 and July 1998. Of these, 132 patients were assigned to TMLR, and 143 patients to continued medical therapy, of which 46 (32%) crossed over to TMLR.

Perioperative mortality was 5% in the TMLR group and 9% in the crossover group. Intention to treat 12-month survival was not significantly different in the two groups, with survival in the TMLR group at 84% and in the medical group 89% ($p = 0.23$). Perioperative complications were again common – atrial arrhythmias 10%, hypotension 10%, ventricular arrhythmias 12%, myocardial infarction 6%, congestive heart failure 4% and respiratory insufficiency 3%.

Angina improved in a significantly larger proportion of patients in the TMLR group than in the medical therapy group at 3, 6, and 12 months ($p < 0.001$ for all three comparisons). At 1 year, 76% of patients in the TMLR group had a 2+ reduction in angina class compared to only 32% in the medical therapy group ($p < 0.001$). In an intention to treat analysis, the Kaplan-Meier estimate of survival free of cardiac events at 1 year was significantly higher in the TMLR group than in the medical therapy group (54% vs 31%, $p < 0.001$). Hospital admissions during the year were also less in the TMLR group than for the medical therapy patients (39% vs 67%, $p < 0.001$). Patients used significantly less anti-anginal medication following TMLR. Myocardial perfusion was measured at baseline and 12 months by nuclear scintigraphy: no significant differences were detected at baseline and at 1 year. Nor were significant differences detected in either fixed defects or ischemic segments.

The results were similar to the Texas Heart Institute results with regards to operative risk and symptomatic benefits. The main difference was in the lack of improvement in perfusion detected by nuclear scintigraphy.

Schofield et al undertook a randomized controlled single-center trial at Papworth Hospital, Cambridge, UK.[27] The entry criteria were again similar to the USA trials. Patients, with severe angina and unsuitable for conventional revascularization, were randomly assigned either to TMLR and normal medication or to medical management only. A total of 188 patients were enrolled and followed up at 3, 6 and 12 months. The mean hospital stay for TMLR was 10.5 days. Perioperative mortality was 5%. Operative morbidity was high, and approximately two-thirds of patients experienced at least one complication (wound and respiratory infections, atrial fibrillation, left ventricular failure) although most were more minor. Twelve-month survival was 89% in the TMLR group and 96% for the medical management group ($p = 0.14$).

TMLR had a significant effect on CCS angina class. A reduction of 2+ angina classes was achieved in 34%, 22% and 25% at 3, 6 and 12 months for the TMLR patients, compared to only 3%, 4%, and 4% in the medical management patients ($p < 0.001$). The difference in exercise times between the two groups was not significant at any time during follow up, and the TMLR group only achieved on average about 40 seconds longer on the treadmill. TMLR patients were able to walk further in the 12-minute walk, which was significant at 3 and 6 months but not at 12 months. There was no difference in hospital admissions between the two groups at 12 months.

The radionuclide myocardial perfusion

scans showed a reduction of the number of reversible ischemic segments in both groups at 3, 6, and 12 months but no difference between the two groups (p = 0.975). There was a small excess of sites with irreversible ischemia among the TMLR patients (p = 0.046). No significant changes in left ventricular ejection fractions were recorded. The results of this trial were important in that the benefits shown by TMLR were considerably less than in previous studies and significantly less than in the randomized USA trials published about the same time.

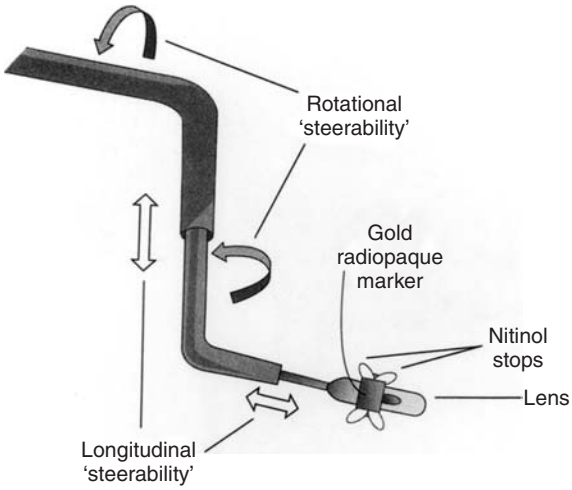

Figure 14.3
PMR fibreoptic laser and delivery device (cardiogenesis). A flexible 400 μm fiberoptic catheter allows easy maneuverability to target left ventricular territory.

Percutaneous myocardial revascularization

Original TMLR CO_2 lasers utilize a quartz crystal that requires a rigid surgical handpiece. Access to the myocardium therefore necessitated open-heart surgery. Advances in the technology of flexible fiberoptic lasers meant the possibility of performing TMLR via percutaneous access: percutaneous myocardial revascularization (PMR). Holmium:YAG and excimer fiberoptic lasers were incorporated into catheters that could be delivered into the left ventricular cavity (Fig. 14.3). Currently, there are two percutaneous laser devices in current use, both using a holmium:YAG fiberoptic laser. As opposed to TMLR, the systems are developed to create laser channels from inside the left ventricular cavity. The channels are bored through the myocardium to a pre-specified depth, to avoid complete penetration of the myocardium.

The main difference between the two systems involves the method of positioning of the laser channels. The CardioGenesis system uses biplane fluoroscopy. The laser catheter tip is carefully positioned at right angles to the required treatment zone before firing the laser (Fig. 14.4). The position is marked on transparencies which overlie the viewing screens.

The Biosense system uses an electromagnetic NOGA™ mapping system, which places an ultra-low magnetic field around the area of the heart. The mapping catheter contains a miniature passive sensor embedded in the tip, which can be located accurately within the magnetic field. The information is then interfaced with a processing unit, which displays the results on a computer screen. The catheter which houses the sensor is similar in structure and size (7 French) to a regular electrophysiology catheter and possesses a deflectable tip, which allows access around the ventricular cavity.

Three-dimensional reconstructions of the

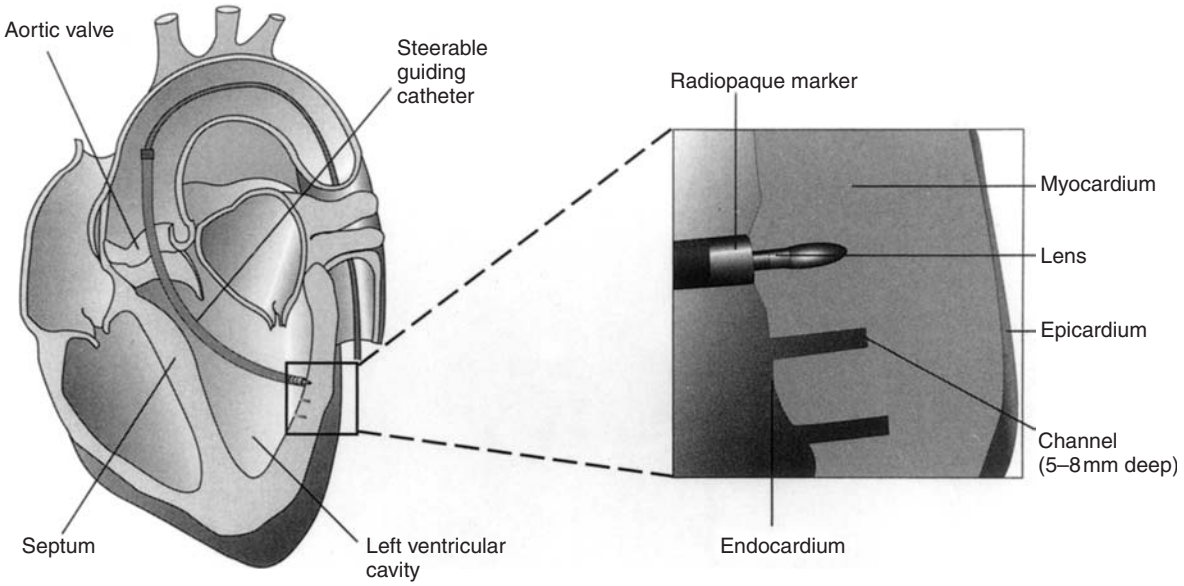

Figure 14.4
PMR fiberoptic laser-tipped catheter positioned in left ventricle cavity. Depiction of ECLIPSE surgical technologies device.

ventricular cavity are displayed on the computer screen by recording 50–150 points around the subendocardial cavity. The computer system then interpolates between a triangular set of points, by estimating the voltage and movements between each point and color coding this on the computer screen. An electromagnetic voltage map and a local shortening map of the left ventricle are created (Fig. 14.5).

These maps are used to assess the areas required for treatment. The laser catheter, which also contains a magnetic field sensor, is introduced into the left ventricle. Accurate positioning of laser channels in then possible throughout the treatment areas.

PMR trials

The results of the PACIFIC trial were reported in the Lancet in Nov 2000 by Oesterle et al.[28] The trial enrolled 221 patients with class III or IV angina who were randomized either to PMR and or to medical treatment only. Exercise tolerance on treadmill at 12 months was found to have increased by a median of 89 seconds with PMR, compared to 12.5 seconds with medical treatment only (p = 0.008). Angina class was class II or lower in 34% of PMR patients compared with 13% of those treated medically. Significant improvements in quality of life measures using the Seattle Angina Questionnaire were also observed. PMR was also associated with low rates of mortality and morbidity. The overall results

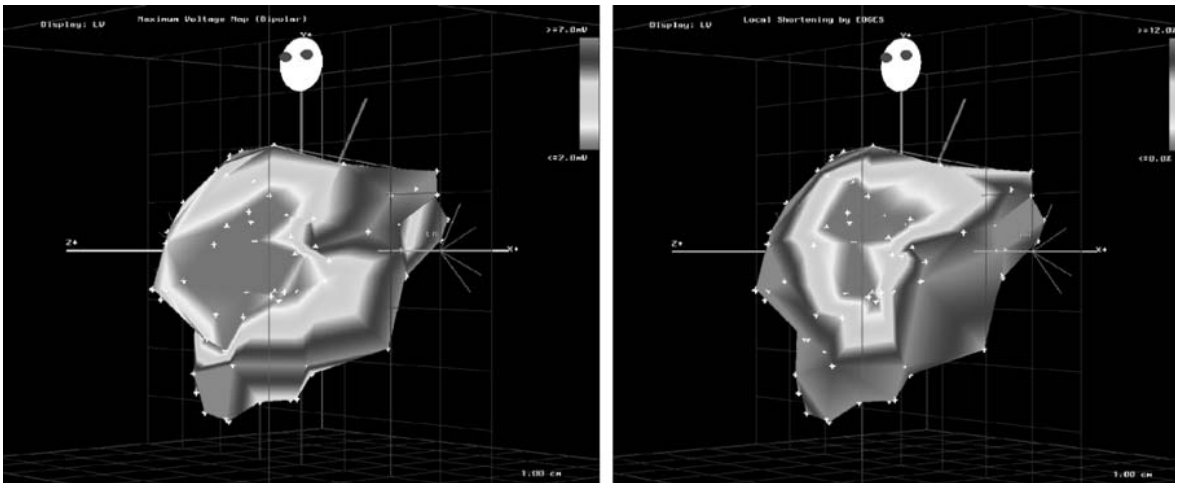

Figure 14.5
PMR with electromagnetic mapping system: (left) electromagnetic voltage map and (right) a local shortening map of the left ventricle following LAD ligation.

were favorable but again the placebo effect of the procedure was difficult to quantify.

A longitudinal study was undertaken at St Thomas' Hospital in London, UK, between May 1998 and September 1999.[29] Twenty-seven patients, with CCS class III or IV angina and who were also unsuitable for conventional revascularization, underwent PMR. Angina class pretreatment was 3.45 ± 0.3 (mean ± SD). At 3 months, this had improved to 2.09 ± 0.6 ($p < 0.001$). There was at a 2+ class improvement in 67% of patients. The improvements were maintained to 6 months but thereafter a gradual return of symptoms was reported. At 1 year there was still a significant improvement in angina ($p < 0.05$), but at 2 years angina levels had virtually returned to baseline (Fig. 14.6). Exercise capacity increased from 342 ± 202 seconds pre-PMR to 470 ± 252 seconds at 3 months ($p < 0.01$). The improvements peaked at 6 months and were still significant at 1 year. A gradual drop off at 2 years was seen. (Fig. 14.7). Quality of life measures were significantly improved at 3 months ($p < 0.01$), with the benefits maintained to 2 years ($p < 0.01$). The findings suggest significant initial symptomatic benefits lasting to 6 months, after which there is a gradual return in symptoms, with no significant anginal improvement 2 years after the procedure. Quality of life benefits are however maintained in the longer-term. These findings call into question how worthwhile the treatment is long-term.

The DIRECT study results were presented at the American Heart Association meeting in New Orleans in November 2000. This was the first study to have a blinded placebo control group with which to compare the results of laser treatment. Inclusion criteria were as previous trials. A total 300 patients were randomized in 14 centers throughout the US. All

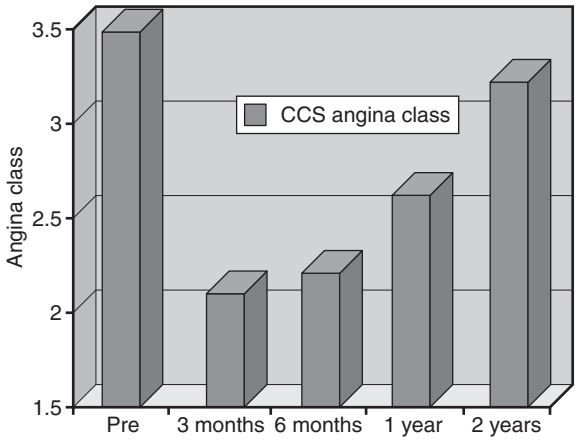

Figure 14.6
St Thomas' PMR study: results of CCS angina class changes. Reproduced with permission from Allen et al.[29]

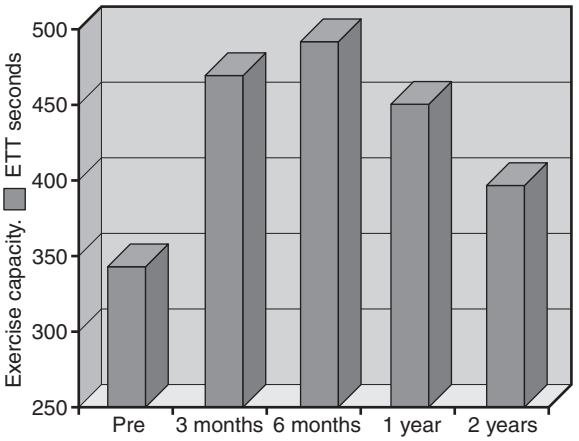

Figure 14.7
St Thomas' PMR study: results of exercise treadmill tolerance. Reproduced with permission from Allen et al.[29]

patients underwent coronary angiography and an LV electromagnetic map and were then randomized either to placebo 'mock procedure', low dose laser channels (10–15 channels/zone), or high dose laser channels (20–25 channels/zone). Patients were sedated and had blindfolds and earphones, so were entirely unaware which treatment arm they had been assigned. Primary endpoint was exercise treadmill duration at baseline and 6 months. Secondary endpoints included changes in angina class and quality of life measures.

The results presented showed improvements in exercise times in all groups but no significant differences between the three groups. Angina class and quality of life improved significantly in all groups, but again showed no difference between the three. There were increased adverse clinical events associated with laser treatment at 30 days, but there were no differences at 6 months. The findings from DIRECT suggest no clinical benefit associated with laser channel treatment. The blinded control group demonstrated a large placebo effect on patients undergoing a 'new laser treatment'. It was suggested that this might account for the benefits demonstrated in the previous trials.

Mechanisms of action

Medical history and current medical practice is full of treatments in which the mechanisms of action are not clearly understood. For example, alternative medicines are a rapidly expanding field that have proved effective to large numbers of people but which often have no known scientific basis to their undeniable benefits. There is still however a large amount of justified scepticism in mainstream medicine towards treatments that lack good experimental evidence of their benefits and methods of action. Current medical practice is leaning more and more towards 'evidence-based

medicine' by which doctors and medical authorities can set guidelines for treatment. As the costs of medical care rise exponentially, funding is targeted at treatments that have been proven to be effective. This means that new treatments, often expensive due to development costs, have to show significant benefits over existing methods of treatment. New treatments are also required to have a scientific basis to their mechanisms of action to support the medical benefits.

Laser revascularization procedures have struggled to gain significant headway in mainstream clinical practice. Positive clinical trials have been reported for over 15 years, yet it is still not widely accepted as an alternative method of myocardial revascularization. The reasons are probably twofold. The marked placebo effects of undergoing a new laser operation are difficult to quantify. Secondly, the mechanism(s) of action are still not understood and are proving elusive to assess with current techniques. Several mechanisms have been postulated and it may be that a combination of them is responsible for the reduction of symptoms. The four most likely mechanisms of action are described below.

Direct perfusion

The original intention behind creating laser channels through myocardium was to perfuse the muscle directly from the ventricular cavity. However, controversy still exists about the fate of these myocardial laser channels. Early studies suggested longterm patency of the channels. Mirhoseini et al demonstrated patent channels in 6 out of 10 patients by follow-up left ventriculography.[21] Dye could be clearly seen to protrude out of the cavity into the channels.

Whittaker and colleagues were able to demonstrate patent channels in rat hearts a month after holmium:YAG laser or needle-treated hearts.[30] Histologic analysis revealed the majority of channels retained a patent lumen, which contained both red blood cells and a blue pigment injected into the circulation prior to autopsy. Pigment was also demonstrated in surrounding tissue which had been rendered 'non-perfused' by coronary artery occlusion. Vessels were observed connected to the patent channels. The channel lumens were all smaller than the 400 μm diameter optic laser fiber or needle used to create them. Several of the laser channels had been completely occluded by fibrosis. Experiments by Whittaker and colleagues demonstrated myocardial ischemic protection from the channels. It was suggested that these findings could be explained by direct flow from the ventricular cavity to the ischemic tissue via patent channels.[30]

In 1997, Mack and colleagues published results of histologic analysis on sheep hearts comparing lasered and non-lasered channels.[20] The sheep were sacrificed at 30 days. Of the lasered channels, 50–60% were identifiable, all of which appeared to represent a 'channel derivative' with evidence of an endothelialized lumen, whereas none of the non-lasered channels had evidence of channel patency ($p < 0.005$). The cross-sectional diameter of the channel derivatives' lumen ranged from 10 μm to 100 μm. The non-lasered channels had no visible remaining lumen and all appeared to be consolidated with inflammatory infiltrate. The investigators also noted a marked neovascular response around the lasered channels, which was absent in the non-lasered channels. Their conclusions were that the endothelial-lined 'lacunae' were formed from

thrombus-filled channels that acutely occlude the channel. They suggested that in some way the laser tissue injury stimulates growth factors, which serve to endothelialize the laser tracks and also induce collateral vessel growth via angiogenesis in the surrounding tissues.

Several other large animal studies have also demonstrated that TMLR results in persistence of 'patent' laser channels at various time intervals from creation.[31–33] Cooley et al reported anatomic evidence of channel patency in a patient who died after a post-TMLR survival period of 94 days.[34] There is a multitude of information that suggests longterm channel patency. However these results are contradicted by just as much information which suggests that channels occlude within a short period of time.

In 1997, Fisher and colleagues[35] published the results of their histologic analysis of TMLR channels, which compared CO_2 with holmium:YAG lasers. They created transmyocardial channels in dog hearts and these were examined histologically at 6 to 24 hours, 2 to 3 weeks, and after 6 weeks of creation. Regardless of the laser type used, they observed that the channel lumen are occluded by fibrin thrombus in the acute setting. Over the subsequent weeks, the channels appeared to be organized by the ingrowth of new vessels and fibroblasts, similar to the generalized healing response typical of other organs. The fibroblasts laid down collagen, which resulted in occlusion of all the laser channels by fibrosis. The holmium:YAG laser produced greater thermoacoustic tissue damage, but by 6 weeks the channel appearances were indistinguishable from those made with the CO_2 laser. The investigators concluded that direct perfusion through patent channels was not feasible and that there appears little longterm difference in the type of laser used.

In 1997, Gassler and colleagues published the histologic findings on three patients who died after 3, 16 and 150 days following TMLR.[36] None of the patients had experienced clinical benefit from the treatment. At 3 days, the laser-created channels were occluded with abundant granulocytes, and thrombocytes. No patent channels were detected. Histologic sections at 16 and 150 days post-TMLR showed no patent endothelialized channels that linked with the left ventricular cavity.

Despite numerous and extensive studies, some of which are mentioned above, channel patency remains a subject of considerable controversy. The majority of work has obviously been done with animals, however histology of human hearts post-TMLR appears to show no real differences. The weight of evidence suggests that the likely course of events involves the majority of laser channels occluding with thrombus shortly after creation. The thrombus is, in time, replaced by fibrous scar with little or no evidence of a lumen remnant. The use of different laser sources and differing energy delivery makes no difference to the likelihood of channel patency. Non-laser methods of channel creation also result in early lumen occlusion. It suggests that the symptomatic benefits observed following TMLR are not the result of direct perfusion from the ventricular cavity to the myocardium via patent channels, even if this were hemodynamically possible.

Angiogenesis

With increased recognition that laser channels are unlikely to conduct significant amounts of blood, it has become evident that human

physiology does not mimic the reptilian. The hypothesis of laser energy dissipation as a cause of tissue injury which leads to the localized stimulation of new vessel formation, or 'angiogenesis', was postulated.

Kohmoto, Yamamoto and colleagues reported evidence of angiogenesis in normal canine hearts as a result of TMLR.[37,38] Ischemia was created in 14 dogs by proximal left anterior descending coronary ameroid constrictors. TMLR was performed in the anterior LV wall (approximately 1 channel/cm^2) of seven dogs. The researchers noted relatively large, mature arterial vessels found frequently within the core of the channel remnants, clearly visible with smooth muscle actin immunostaining. Their high density within the channel remnant suggested that these were new vessels and therefore the result of a significant angiogenic process. The results showed a four times greater degree of new vessel formation in the TMLR group ($p < 0.001$) as against a control ischemic tissue. There was also evidence of more neovascularization in the myocardium adjacent to the TMLR channel remnants ($p < 0.001$).

Fisher and colleagues reported similar evidence of angiogenesis in dogs following TMLR.[35] The canine heart is well known to have a propensity to develop collaterals as a response to myocardial ischemia[39,40] and therefore may not be the best model for human hearts. Malekan and colleagues investigated the possibility of angiogenesis in ovine myocardium following TMLR.[41] They investigated the histologic changes seen following channel creation with a CO_2 laser compared to those formed by use of a power drill. There was obliteration of all channel lumen. All original channels were replaced with granulation tissue and fibrosis with scattered chronic inflammatory cells, composed predominantly of lymphocytes and histiocytes. However, an increase in the number of vessels with one or more layers of smooth muscle cells was highlighted by Verhoeff-Van Gieson (elastic) stain. These blood vessels were seen within the channel remnant and the area immediately surrounding the channel remnant. Red blood cells were seen within these luminal spaces, which suggested flow of blood through them. The degree of angiogenesis created by either source was quantified by counting the number of vessels by high power microscopy. Both CO_2- and powerdrill-treated areas had significantly higher densities of vessels than non-treated areas, with no significant difference between the two treatments. These findingssuggested that angiogenesis does occur following TMLR, but is the result of normal tissue inflammatory response to injury and is not specific to laser-induced thermal injury.

In contrast to these findings, Mack et al reported marked neovascular response around lasered channels in comparison to non-lasered channels, which suggests that laser energy may be an important component of angiogenesis and therefore of clinical benefit.[20] Gassler and colleagues demonstrated histologic evidence in human hearts that showed all laser channels occluded shortly after TMLR.[36] There was, however, evidence of extensive capillary networks within the healed fibrinous scar of laser channels at 150 days after creation.

A vast amount of histologic evidence has been reported, some of which has been mentioned above. A lot of the findings are contradictory. However, a pattern of the likely changes following laser channel creation emerges. Following laser energy dissipation, the surrounding myocardial tissue is vaporized to create a lumen. Further energy dissipation

into the surrounding tissues results in localized necrosis around the channel lumen. The degree of myocardial necrosis is dependant on the type of laser used. Healing processes appear to depend upon the type of myocardial tissue and the ischemic state of the myocardium. In humans, a localized inflammatory response is evident within days of the procedure and persists for about 4 weeks. Inflammatory cells have been shown to be responsible for the liberation of several growth factors (e.g. vascular endothelial growth factor [VEGF] and basic fibroblast growth factor [bFGF]) and cytokines, which are in turn responsible for the promotion of angiogenesis (and for up-regulation of receptors for these factors. The general features of such a response are likely not to be unique to laser injury but would be expected with any type of injury that affected a similar amount of myocardium. These events stimulate budding and growth of small vessels, 'true angiogenesis',[42] and remodelling of pre-existent vessels by endothelial and smooth muscle cell proliferation, which may potentially lead to larger vessel lumens.[42]

If one accepts that a degree of angiogenesis does occur, that results in increased capillary densities in the treated myocardial areas, the next important question is whether this could lead to improvements in myocardial blood flow. Unfortunately myocardial perfusion is extremely difficult to measure accurately and the methods presently available are unlikely to be able to detect truly or consistently the small changes in perfusion or microperfusion that may occur following treatment. The other difficulty is that myocardial blood flow changes over time without any intervention and is also dependent on a multitude of variable influences. This would explain the many contradictory reports on perfusion changes after TMLR in the studies published. More accurate methods of assessing myocardial perfusion that use cardiac magnetic resonance imaging and positron emission tomography are being developed which will hopefully shed further light on the subject.

Denervation

Another potential mechanism of action that has been investigated is the denervation of myocardial nerve fibers as a result of localized laser tissue injury. Cardiac visceral nerve fibers, the δ and C fibers, which convey the pain of angina, travel alongside the cardiac sympathetic afferent fibers en route to the central nervous system.[43] Postganglionic sympathetic and preganglionic parasympathetic fibers combine at the base of the heart to form the cardiac plexus with its dorsal and ventral parts.[44–46] The plexus gives rise to large nerves that course along the major arteries to innervate cardiac structures. The afferent and efferent sympathetic fibers are located in the superficial subepicardium, primarily in the periadventitia of the coronary arteries, and dive intramurally to innervate the endocardium.[45] They can be interrupted by epicardial lesions at the atrioventricular groove and within the ventricle, which causes 'downstream' efferent sympathetic denervation. It could therefore be postulated that laser energy dissipation into the myocardium could result in damage to these nerve fibers and result in the reduction of angina sensation.

The denervation of ischemic myocardium following laser revascularization would explain very well the immediate reduction in symptoms that has been reported.

Problems again, however, arise when trying

to assess myocardial denervation, which, as with myocardial perfusion, is very difficult to quantify accurately. In the 16th century, William Harvey demonstrated to Charles I that the heart was insensitive to pain.[47] The subject of this observation was the son of Count Montgomery, a young man who had miraculously survived an injury to his ribs and costal cartilages that left the beating heart exposed in an open cavity whilst he was still conscious. Harvey observed that neither pricking nor pinching the epicardium evoked any sense of discomfort and concluded that the heart was entirely free of sensory innervation. It is now understood that this misconception arose because of the paucity of sensory endings in the heart. Spatial summation is necessary to activate a sufficient number of nerve fibers in order to breach the threshold.[43] This is the mechanism by which ischemia causes angina.

Kwong and colleagues published their results into denervation in canine hearts following laser channel creation.[49] A left thoracotomy was performed in 16 dogs. Treatment groups included animals in which a portion of the left ventricle underwent TMLR with a holmium:YAG laser or chemical destruction of cardiac nerves by application of phenol to the epicardium. Sham-operated negative control animals underwent thoracotomy and pericardiotomy alone. Cardiac nerve function was assessed by epicardial application of bradykinin, a potent algesic, before treatment and 2 weeks after the operation. Cardiac innervation of treated and untreated left ventricular myocardium was further assessed by immunoblot analysis performed with an antibody against tyrosine hydroxylase, a sympathetic nerve specific enzyme. The laser- and phenol-treated areas appeared to be virtually entirely denervated, compared to the controls. These results suggested that laser channels do destroy cardiac nerve fibers, which may contribute to the reduced sensation of angina that is seen following TMLR.

Denervation of ischemic myocardium following laser revascularization is a credible mechanism to reduce angina. The concern is that this would result in silent ischemia and loss of the protective warning of angina. Whether or not this is such a detrimental occurrence is also debatable. There is a lot of historical evidence to suggest that denervation does not result in increased likelihood of myocardial infarction or sudden death.[43,49] Cardiac sympathectomy operations, which were in vogue in the 1950s, often resulted in improved life expectancy and far more active lifestyles as a result of relief of severe angina.

Another interesting point is that one would expect a degree of nerve regeneration to occur and therefore a return in symptoms in time, which has been noted in human studies[23] with longer follow-up periods.

The possibility of denervation occurring in combination with angiogenesis cannot be ruled out. It would explain early benefits in symptoms as well as the improvements in perfusion that have been reported.

Placebo effect

The most difficult aspect to the introduction of any new treatment is often the assessment of how much the benefits seen are due to the placebo effect. Double blind clinical trials have reported improvements based solely on placebo effect in between 25% and 75% of patients. The complaints that have been found to benefit most, as one would expect, include chronic pain syndromes and disorders which

have a large cerebral component to their effects on patients. This certainly includes angina. Undergoing a 'new laser treatment' for patients who have chronic angina will carry a large placebo effect. The main difficulty is assessing to what extent this has affected the benefits seen in TMLR/PMR. The recently published DIRECT findings suggest that all the improvements seen could be entirely put down to placebo benefit. However, placebo effects tend to be maximal almost immediately after treatment and have been found to diminish over the following 6 months. This is not the pattern of improvements observed in most of the TMLR/PMR studies.

Summary

A significant proportion of patients with severe angina symptoms are currently unsuitable for conventional methods of revascularization. Laser channels potentially offer an alternative method of perfusing ischemic myocardium. Studies have consistently shown marked improvements in symptoms. The main concern remains whether the treatment is just an expensive and effective placebo, or whether a true benefit exists over and above the placebo effect.

The other contentious issue remains the potential mechanism of action. The concept of angiogenesis has caused considerable amounts of excitement among the proponents of laser revascularization techniques. If angiogenesis were to occur to a sufficient degree as to improve perfusion, then this would be expected to provide a lasting and effective method of protecting ischemic myocardium. It would be a significant medical breakthrough in the treatment of ischaemic heart disease and could lead to far wider therapeutic options.

The inevitable conflict of interests that arises when investigators may benefit from positive findings whose interpretation is difficult. Angiogenesis has been strongly advocated as the mechanism of action by laser technology companies and by several influential investigators. However the evidence is not yet clear enough to suggest anything more than normal healing processes which produce a disorganized neovascularization that is unlikely to improve perfusion. Another important point is that the timecourse of symptom improvement, following laser treatment, does not concur with angiogenesis. The improvements in symptoms noted have been early with no subsequent enhancement over time that would be expected with the development of a vascular network.

The DIRECT study results no doubt inflict a severe knockback to laser revascularization. There are still, however, several issues that need resolving. The size of the channels created in this study were smaller than some other trials and this may well be a factor. Placebo effects tend to be greatest for the first few months and it will be interesting to see if there is any difference in longer term follow up. Injection of vascular growth factors into channels also offers possible further avenues of progress. This is not the last word on the subject of laser revascularization.

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15

Vascular Brachytherapy

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Introduction

Restenosis remains the major limitation of percutaneous, catheter-based interventional therapy. Endovascular radiation therapy, also known as vascular brachytherapy, represents a relatively new and promising tool to overcome this limitation. Brachytherapy is derived from the Greek 'brachy' (meaning 'short') and 'therapy' and describes the application of radioactivity by a sealed source at a very short distance to the target tissue, e.g. by intracavitary or interstitial source placement. It has the benefit that very high doses of radiation can be delivered almost directly to the target. Radiation therapy has been proven successful in the treatment of hypertrophic scars, keloids, heterotopic bone formation, ophthalmic pterygia and solid malignancies.

Clinical studies

In 1964, Friedman reported on the first in vivo use of intravascular radiotherapy.[1] The first clinical trial was initiated in 1990 in patients with in-stent restenosis of femoropopliteal arteries using gamma (^{192}Ir) radiotherapy.[2] Human coronary arteries were treated for the first time by Condado et al in 1997: de novo lesions where treated by balloon angioplasty followed by gamma-radiation (^{192}Ir). No restenosis was observed after 6 months.[3] Also in 1997, Teirstein demonstrated the effectiveness of gamma therapy for the treatment of in-stent restenosis,[4] whilst Verin reported the feasibility of beta sources after balloon angioplasty.[5] A considerable number of randomized clinical trials have now provided evidence of the efficacy of radiation therapy.

Catheter-based line sources

Gamma radiation therapy is the only treatment so far shown to reduce restenosis in randomized, double blind, placebo-controlled trials (Table 15.1) Most of the ongoing trials use catheter-based beta-radiation sources (Tables 15.2, 15.3). Overall, the initial target has been the treatment of de novo coronary stenosis. However, recent design trials have included patients with restenotic lesions.

Radioactive stents

Clinical trials that utilize radioactive stents have been disappointing, despite effective prevention of neointimal growth with the stent. Clinical and angiographic outcome has been hampered by restenosis at the edges of the radioactive stent, coined the 'candy wrapper' effect. This unfavorable phenomenon occurs

Study	n	*Dose (Gy)*	*Lesion length (mm)*	*Source*	*Restenosis rate*	*MACE rate*
SCRIPPS[4]	53	8–30††	<30	^{192}Ir	17	15
				Placebo	54	48
WRIST[6]	130	15*	<47	^{192}Ir	22	29
				Placebo	60	68
Long WRIST[7]	120	15*	36-80	^{192}Ir	46	N/A
				Placebo	78	N/A
GAMMA-1[8]	252	8–30††	<45	^{192}Ir	32	28
				Placebo	55	44
GAMMA-2	125	14*	<45	^{192}Ir	34	30

MACE = major cardiac events
N/A = not available
* Dose at 2 mm from the source
†† to external elastic membrane

Table 15.1
Results of placebo-controlled gamma radiation trials at 6-month follow-up.

Study	n	*Dose (Gy)*	*Lesion criteria*	*Lesion length (mm)*	*Source*	*Sponsor*
ARREST	50	<8, <35**	De novo	<=25	^{192}Ir	Vascular Therapies
ARTISTIC	50	12, 15, 18*	In-stent restenosis	<=25	^{192}Ir	Vascular Therapies
BERT[9]	20	12, 14, 16†	De novo	<=15	^{90}Sr/^{90}Y	Novoste
BERT 1.5	31	12, 14, 16*	De novo	<20	^{90}Sr/^{90}Y	Novoste
Betacath	1,456	0, 14,18*	De novo,			
			Restenotic	<20	Sr/^{90}Y	Novoste
BetaWRIST[10]	50	20.6‡	In-stent restenosis	<=47	^{90}Y	Boston Scientific
BETTER	150	20‡	De novo, restenotic	<=25	^{32}P	Radiance
BRIDGE	100	0, 20†	De novo	<=15	^{32}P	Guidant
BRIE[11]	13	14, 18*	De novo,			
			Restenotic	<20	^{90}Sr/^{90}Y	Novoste
Compassionate						
Use Rotterdam[12]	22	16, 20†	In-stent restenosis	<30	^{90}Sr/^{90}Y	Novoste
CURE	30	20‡‡	De novo	<22	^{188}Re	Columbia University
Dose Finding[13]	181	9, 12, 15, 18‡	De novo	<15	^{90}Y	Schneider
GAMMA-1[7]	252	0, 8-30††	In-stent restenosis	<=45	^{192}Ir	Cordis
GAMMA-2	125	14*	In-stent restenosis	<=45	^{192}Ir	Cordis

Table 15.2
Intracoronary brachytherapy trials. (continued overleaf.)

GAMMA-3	280	14*	In-stent restenosis	<=45	^{192}Ir	Cordis
Geneva[5]	15	18‡	De novo	<29	^{90}Y	Schneider
GRANITE	100	14*	In-stent restenosis	<=45	^{192}Ir	Cordis
INDIRA	800	0, 11••	De novo,			
			In-stent restenosis	<=30	^{192}Ir	Cordis
INHIBIT[14]	360	0, 20†	In-stent restenosis	<44	^{32}P	Guidant
IRIS[15]	37	5–12•	De novo,			
			Restenotic	<28	^{32}P	Isostent
LongWRIST	120	0, 15*	In-stent restenosis	>80	^{192}Ir	Cordis
MARS	35	20 Gy†	De novo	<20	^{188}Re	Mallinckrodt
PERTH	100	18‡	In-stent restenosis	20–80	^{188}Re	Royal Perth Hospital
PREVENT[16]	37	0, 28, 35, 42†	De novo,	<22	^{32}P	Guidant
			Restenotic,			
			In-stent restenosis			
^{32}P Dose Response[17,18]	162	45–92•	De novo,	<28	P-32	Isostent
			Restenotic,			
			In-stent restenosis			
^{32}P Dose	50	22–92•	De novo,	<15	^{32}P	Isostent
Response			Restenotic			
Cold Ends						
^{32}P Dose	50	71–126•	De novo,	<15	^{32}P	Isostent
Response			Restenotic			
Hot Ends						
Radiation Stent	30	52–106•	De novo,	<13	^{32}P	ACS
Safety Trial			Restenotic			
RENO	1000	14–20*	De novo, Restenotic,	Not limited	^{90}Sr/^{90}Y	Novoste
		16–22*	In-stent restenosis	Not limited	^{90}Sr/^{90}Y	
SCRIPPS-1[19]	55	0, 8–30††	Restenotic	<30	^{192}Ir	Cordis
SCRIPPS-2	100	0, 8–30††	In-stent restenosis	<65	^{192}Ir	Cordis
SCRIPPS-3	500	0, 14*	In-stent restenosis	<81	^{192}Ir	Cordis
SMARTS	180	12*	De novo	<=25	^{192}Ir	Vascular Therapies
START	476	0, 16, 20*	In-stent restenosis	<20	^{90}Sr/^{90}Y	Novoste
START 40/20	206	16, 20*	In-stent restenosis	<20	^{90}Sr/^{90}Y	Novoste
SVG WRIST	120	0, 15*	SVG	<=45	^{192}Ir	Cordis
Venezuela[3]	21	19–55***	De novo,	<30	^{192}Ir	Non commercial
			Restenotic			
WRIST[6]	130	0, 15†	In-stent restenosis	<=47	^{192}Ir	Cordis

* at 2 mm into the vessel wall
** with IVUS guidance
*** at 1.5 mm from the source
† at 0.5 mm into the vessel wall
†† to E.E.M.
• cumulative dose over 100 days delivered to 1 mm depth outside the stent surface
•• at 3 mm from the source
‡ at 1 mm from balloon surface
‡‡ at media

Table 15.2 (cont.)

Study	n	*Dose (Gy)*	*Lesion length (mm)*	*Source length (mm)*	*Source*	*Restenosis rate*	*MACE*
Geneva[5]	15	18.0†	<20	29	^{90}Y	40	33.0
BERT[8]	20	12.0, 14.0, 16.0*	<=15	30	Sr/^{90}Y	15	15.0
BERT 1.5	35	12.0, 14.0, 16.0*	<20	30	Sr/^{90}Y	11	9.0
BetaWRIST	50	20.6‡	<= 47	29	^{90}Y	34	34.0
					Placebo+	71	76.0
BRIE[11]	149	14.0, 18.0*	<20	30	Sr/^{90}Y	34	34.0
Dose Finding Study[13]	181	9.0, 12.0, 15.0, 18.0‡	<15	29	^{90}Y 9 Gy	9	16.0
					^{90}Y 18 Gy	26	13.0
PREVENT[16]	96	16.0, 20.0, 24.0++	<22	27	^{32}P	22	26.0
					Placebo	50	32.0
START	396	18.0, 20.0*	<20	30	Sr/^{90}Y	29	18.0
					Placebo	45	25.9
Compassionate use Rotterdam[12]	18	16.0, 20.0*	<30	30	Sr/^{90}Y	53	47.0

MACE = major cardiac events
* dose at 2 mm from the source
†dose at the inner arterial surface
‡ dose at 1 mm from balloon
++ dose at 1 mm into vessel wall
+ 50 placebo pts from WRIST

Table 15.3
Results of beta radiation trials at 6-month follow-up.

irrespective of the stent design (cold end, hot end) or the dose rate (high activity vs low activity) (Table 15.4).

Basic radiation physics

Radioactivity

Radioactivity is the spontaneous process in which an unstable nucleus, with either too many or too few neutrons, turns to a stable state (ground state) and so releases superfluous energy. This release of energy is called radiation, which can be in the form of electromagnetic waves, such as gamma waves, or of particle rays, such as alpha, beta and neutron rays. This process is often called the 'disintegration' of an atom. Mathematically, the activity (A) can be expressed by the number of disintegrations (dN) within a time interval (dt) ($A = -dN/dt$). In the international system of units (SI), this quotient is called the becquerel (Bq).

Decay

For most atoms, the activity is proportional to the number of atoms ($A = \gamma N$). The proportionality constant is called the decay constant. This leads to the decay law:

Study	n	*Stent activity (μCi)*	*Lesion length (mm)*	*Restenosis (rate)*	*TLR*
IRIS 1A	32	0.50–1.00	<15	31	21
IRIS 1B	25	0.75–1.50	<15	50	32
IRIS Heidelberg	11	1.50–3.00	<15	54	N/A
IRIS Rotterdam	26	0.75–1.50	<28	17	12
^{32}P Dose Response Rotterdam[20]	40	6.00–12.00	<28	44	25
^{32}P Dose Response Milan[21]	23	0.75–3.00	<28	52	52
	29	3.00–6.00		41	41
	30	6.00–12.00		50	50
	40	12.00–21.00		30	30

N/A = not available
TLR = target lesion revascularization

Table 15.4
Results of ^{32}P radioactive stents at 6-month follow-up.

$A_t = A_0 \exp(-\gamma t)$
and $\gamma = \ln 2 / T_{1/2}$.

$T_{1/2}$ is called the 'physical half-life time', being the time that the original activity of a nuclide has been reduced by a factor of two. The physical half-life time is characteristic for nuclides, which are distinct nuclear species, and isotopes, which are various forms of an element.

Biological half-life

Biological half-life describes the time needed by the body to eliminate one-half of an administered amount of any substance by regular process of elimination. This time is approximately the same for both stable and unstable isotopes of the same element.

Absorption – radiation dose

The energy released during transformation of an unstable atom into a stable atom is absorbed in tissue. The quantity of absorbed energy in a tissue is called the 'dose', measured in the SI unit gray (Gy=J/kg). The dose is strongly dependent of the type of radiation (activity and decay) and the time span, also called 'dwell time'.

Radiation dose rate

Dose rate is the dose of radiation per time (delivered or received). The dose rate delivered by a source depends on the activity of the source and the radionuclide that it contains. Currently, all removable vascular brachytherapy sources deliver energy at high dose rate, while radioactive stents deliver energy at low dose rate.

Equivalent dose

The biological effects of the absorbed radiation are dependent on the type of radiation and the type of tissue. This is expressed by weighting factors for the type of radiation and

for the specific organ or tissue. After correction, the dose is called the 'equivalent dose'. In the field of radiation protection measurements, this is the dose used.

Isodose

The isodose is identified by a locus at every point of which the absorbed dose is the same.

Currently used isotopes

The most important physical properties of currently used isotopes in vascular brachytherapy are listed in Table 15.5. These isotopes show important physical differences. Basically, gamma radiation consists of photons, beta radiation of electrons.

Gamma radiation

Gamma rays are photons that originate from the center of the nucleus and take the form of electromagnetic radiation. A heavy unstable nucleus will emit an alpha or beta particle followed by gamma radiation. An alpha particle is a heavyweight charged particle, which can travel only very short distances within tissues. Gamma rays may have either one or two discrete energy values, or a broad spectrum of many energy values. They penetrate deeply within tissues.

From the clinician's point of view, gamma radiation offers the following advantages: it has been proven effective in randomized, double blind, placebo-controlled trials; it penetrates tissue deeply and thus is ideal for large vessel diameters; it does not show attenuation by stent struts and thus is ideal for the treatment of in-stent restenosis.

However, gamma radiation requires extensive shielding (25 mm lead) and implies a high radiation exposure for patient and staff, so that staff must leave the procedure during radiation therapy. Finally, it requires relatively long dwell times (8–20 min).

X-ray radiation

X-rays are comparable to gamma radiation. Their physical characteristics are similar, although their origin is different. While the photons of gamma radiation originate from the nucleus, the photons of X-rays originate from the electron orbit.

Beta radiation

Beta particles are lightweight high-energy electrons, with either positive or negative charge. When beta particles, which can travel only finite distances within tissues, are slowed down by nuclei interactions, they give rise to high penetration X-rays, called 'bremsstrahlung'.

Isotope	*Emission*	*Max. energy*	*Av. energy*	*Half-life*
^{192}Ir	γ	612 keV	375 keV	74 days
^{90}Sr/^{90}Y	β	2270 keV	970 keV	28 years
^{32}P	β	1710 keV	690 keV	14 days

Table 15.5
Isotopes used in vascular brachytherapy.

The rate of interaction of photons with other material is much lower then the interactions with electrons. That means, the energy transfer to other material is less intensive for gamma than for beta radiation. In the setting of brachytherapy, this has two major consequences:

- Dwell time: to obtain a defined dose in a tissue at a certain distance from a source, gamma sources require much higher activities or much longer dwell times in comparison to beta sources. This is because the rate of interactions of gamma radiation (i.e. photons) in tissue is lower than the rate of interactions of beta radiation (i.e. electrons).
- Radiation exposure: because of deep tissue penetration, the exposure to the staff both inside and outside the room is much higher during treatment with gamma radiation than during beta radiation. In consequence, staff should leave the procedure room during radiation treatment and additional shielding facilities have to be implemented.

From the clinician's point of view, beta radiation offers the following advantages: shielding is simple by means of thick plastics; dwell times are relatively short (3–10 min); radiation exposure to the patient only local, the radiation exposure to staff is negligible and thus allows staff to remain in the procedure room during treatment.

However, there is a lack of data concerning its efficacy, except in-stent restenosis; beta radiation is probably not able to treat vessels with diameters >4 mm (with existing devices); the dose distribution shows considerable inhomogenicity (centering device required); and the beta radiation is partially shielded by stents and calcified plaques

Mechanisms of action

Cell biological level

Absorbed radiation can cause damage in tissue either directly by ionization or indirectly by interacting with other molecules to produce free radicals, which will subsequently damage the critical target. Approximately 80% of the radiation damage is caused by these free radicals. The most critical target is DNA. In consequence, early and late toxic effects in normal tissue are mainly caused by cell death.

These biological effects are independent of the radiation type (gamma, beta or X-rays). However, total radiation dose and dose rate are a key factor, since damage caused by radiation can be repaired between fractionated doses or during low dose rate exposure. Furthermore, there seem also to be inverse dose rate effects in human cells, most probably caused by blocking cells in the mitosis (G2) phase of the cell cycle, which is known to be more radiosensitive, by a low dose rate (approx. 6 mGy/min) thereby causing more cell death.

Vascular level

In injured vascular tissue, radiation doses of 12–20 Gy appear to be efficacious in inhibiting neointimal formation. The local mechanisms of action are complex, dose dependent and poorly understood. Possible high-dose radiation effects include selective inactivation of smooth muscle cells and myofibroblasts, or complete elimination of their proliferative

capacity at doses >20 Gy. Application of a lower dose could mean that restenosis would only be delayed for the period of time necessary for the population of smooth muscle cells to regenerate. Furthermore, low-dose radiation (4–8 Gy) even promotes cellular growth.

During clinical application

Balloon angioplasty followed by irradiation predominantly shows an increase in minimal lumen diameter of the treated segment at follow-up.[3] This is in contrast to standard balloon angioplasty, where late lumen loss caused by neointimal growth and vessel shrinkage is the usual response.[22,23] Irradiation inhibits neointimal growth,[24] may prevent shrinkage after balloon angioplasty[25] and even promote positive remodeling of the treated segments.[26]

'Candy wrapper' effect

In contrast, edge segments show an increase in plaque volume without adaptive remodeling.[24,27,28] which causes the 'edge' 'candy wrapper' effect (Fig. 15.1), first described by Albiero et al.[29]

Geographic miss

As suggested by known cell biological effects and animal data, low-dose radiation at the extremities of the source and angioplasty-induced vessel injury, referred to as 'geographic miss' seems to play a key role in edge restenosis and treatment failure for brachytherapy (Fig. 15.2).[12,30]

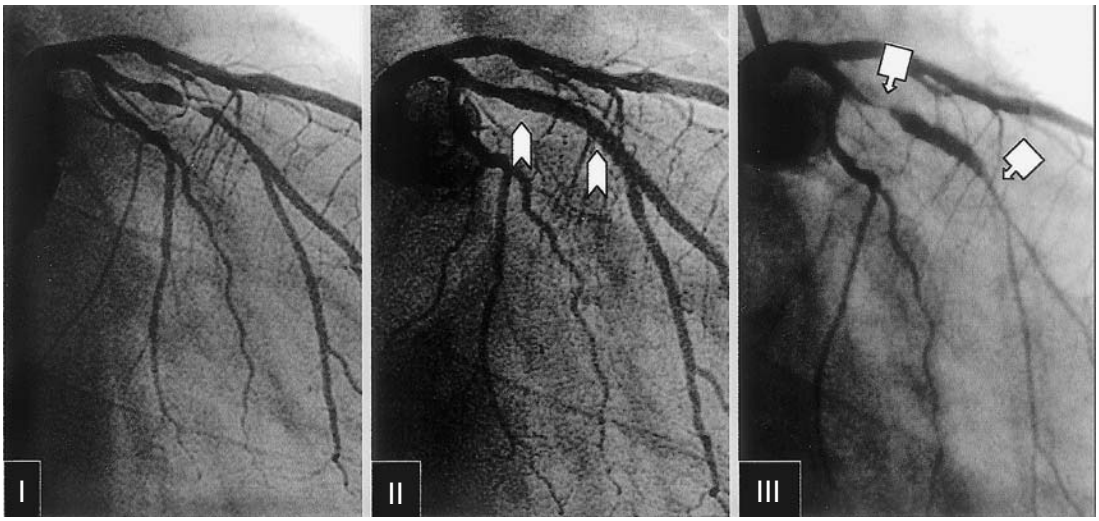

Figure 15.1
'Candy wrapper' effect. Angiogram of the left coronary artery with a significant lesion in the left circumflex artery: (I) before intervention, (II) after implantation of a radioactive stent (ACS radioactive stent, ^{32}P wire, see thin arrows) and (III) at 6-month follow-up. Significant lumen narrowing at the proximal and at the distal extremity of the stent is visible at follow-up, referred as 'edge effect' or 'candy wrapper' effect.

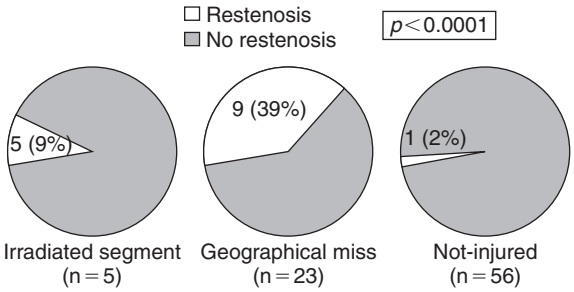

Figure 15.2
Geographic miss: association of restenosis at 6 months after coronary beta radiation therapy and geographic miss. The restenosis rate in the geographic miss segments is significantly higher than in the irradiated segment and the non-injured reference segments (39% compared with 9% and 2%).

Treatment procedures

Devices

In the US, two systems have FDA approval: the Cordis Checkmate and the Novoste Beta-Cath. In Europe, the following three systems are actually in clinical use.

The ^{192}Ir seed train system delivers gamma radiation by means of a multilumen, non-centering catheter (with blind lumen for the source train), which is compatible with a 7F guiding catheter and a 0.014" guidewire. The source is designed as a ^{192}Ir seed train with non-radioactive, X-ray markers at each end (Fig. 15.3). The treatment length is 23 mm

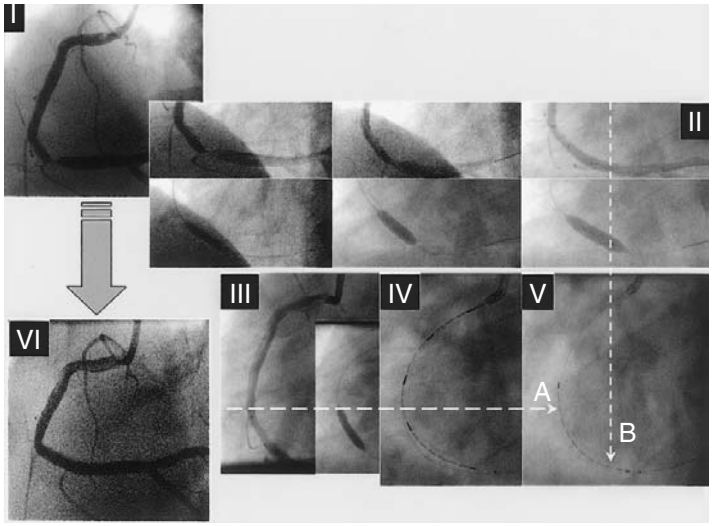

Figure 15.3
Treatment of a lesion in the right coronary artery (I) with ^{192}Ir gamma radiation (Cordis system). The angioplasty procedure entails predilatation, stent implantation (II) and postinflation (III). All balloons have been filmed deflated with contrast injection (II and III, upper images) and at maximum inflation (II and III, lower images) to allow for anatomical orientation. For the assessment of the appropriate source length, a dummy source with radio-opaque markers to indicate length has been introduced (IV). The ^{192}Ir seed train with non-radioactive, X-ray markers at each end is correctly positioned: line A indicates the most proximal balloon position, line B indicates the most distal balloon position within the coronary. The injured segment is completely covered by the source with a safety margin of 1 seed proximal and distal to the injured segment. The final result is given in angiogram VI.

(6 seeds), 39 mm (10 seeds) or 55 mm (14 seeds). The source ribbon is mechanically advanced and withdrawn by a hand-cranked afterloader.

The $^{90}Sr/^{90}Y$ seed train system delivers beta radiation by means of a 5F multilumen, non-centering catheter (with closed lumen for the radiation source train and the fluid return and one open lumen for the guidewire), which is compatible with a 8F guiding catheter and 0.014" guidewire. The source is designed as a $^{90}Sr/^{90}Y$ seed train with a treatment length of 30 mm (12 seeds), 40 mm (16 seeds) or 60 mm (24 seeds). The source train has non-radioactive, X-ray markers at each end (Fig. 15.4). The source ribbon is advanced and withdrawn hydraulically by a hand-held afterloader.

The ^{32}P wire system delivers beta radiation by means of a multilumen, centering balloon-catheter (spiral design) which is compatible with a 7F guiding catheter and a 0.014" guidewire. The balloon length is 32 mm and 52 mm, the balloon diameter 2.5 mm, 3.0 mm and 3.5 mm. The balloon carries X-ray markers at the extremities. The source is a 20 mm-long ^{32}P wire (0.018") sealed at the wire tip. Non-radioactive X-ray markers are placed to bracket 80% therapeutic dose range of the wire proximally and distally to the source. The source wire is computer controlled and is advanced and withdrawn by a high-dose rate afterloader (Fig. 15.5). The system calculates the treatment time automatically and performs an automated pullback of the source (stepping procedure).

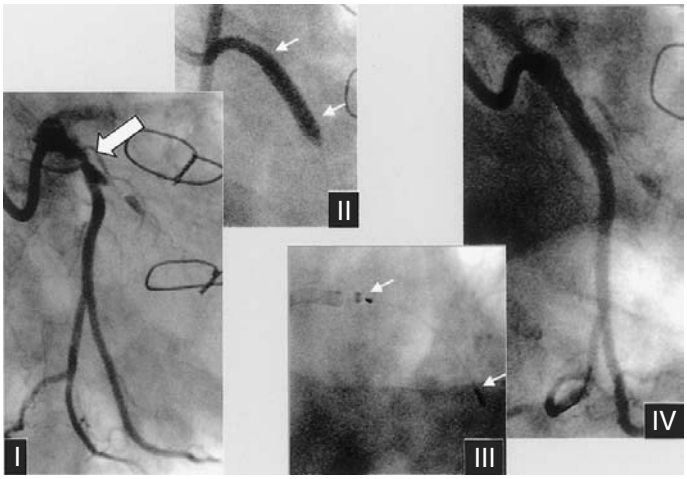

Figure 15.4
Treatment of a lesion in the left circumflex artery (I, arrow) with $^{90}Sr/^{90}Y$ beta radiation. The angioplasty procedure entails direct stent implantation and, the injured segment is assessed by means of radio-opaque balloon markers (II, arrows). The $^{90}Sr/^{90}Y$ beta source with non-radioactive, X-ray markers at each end (arrows) is positioned to cover the injured segment completely with safety margins proximal and distal to the injured segment (III). The final result is given in angiogram IV.

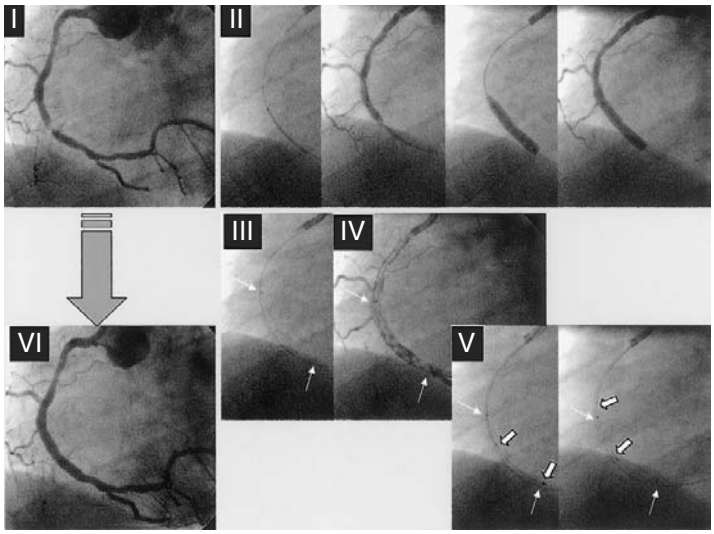

Figure 15.5
Treatment of a lesion in the right coronary artery (I) with ^{32}P beta-radiation. The angioplasty procedure entails direct stent implantation. The stent delivery system has been filmed for anatomical orientation deflated, deflated with contrast injection, at maximum inflation and at maximum inflation with contrast injection (II). The position of the spiral balloon is assessed by means of the X-ray markers at the extremities of the balloon (III, arrows) and by contrast injection (IV). The source wire has X-ray markers at the proximal and distal end (V, thick arrows). Radiation is delivered during an automated stepping procedure with initial source positioning distally (V, left) followed by automated pullback (V, right) The final result is given in angiogram VI.

Patient selection

To date, there exists no established indication for brachytherapy. Potential indications include all circumstances with elevated risk for restenosis after conventional catheter-based intervention, such as long lesions, saphenous vein grafts, small coronary arteries, in-stent restenosis, multivessel disease, diabetic patients and renal insufficiency patients. Contraindications are previous radiotherapy of the chest, previous intracoronary brachytherapy, pregnancy, and genetic radiation sensitivity disorders (e.g. ataxia-telangiectasia).

Medication

At the beginning of the procedure, neuroleptics and analgesics should be administered. Repeat bolus is given during the procedure, if needed. This is especially helpful when using an afterloading technique, as it prolongs procedural time and creates significant ischemia during radiation in the majority of the patients. In addition, aspirin 325 mg intravenously and heparin 10 000 IU should be administered immediately after arterial sheath placement. Activated clotting time (ACT) should be checked every 30 minutes after the

first bolus injection in order to maintain ACT > 300 s. Additional heparin is given if necessary.

During the procedure, glycoprotein IIb/IIIa receptor blockers are given deliberately in patients with unstable angina, periprocedural intracoronary thrombus formation or dissection.

Set-up

For the angioplasty procedure, a standard angioplasty set is needed.

For brachytherapy, the catheterization laboratory must have appropriate shielding. An example of shielding and dose calculation is given in Fig. 15.6. The radiation oncologist prepares the brachytherapy device (e.g. check for mechanical integrity, dummy source, etc). For this purpose, an extra sterile table and light is recommended. A 'bail-out' box must be in the procedure room, consisting typically of an assortment of long-handled instruments for grasping a source and of a shielded container (lead for gamma radiation, plastic for beta-radiation source) to place the source safely. Radiation detectors to survey the environment during the procedure and contamination monitors to detect source leakage are needed. At least two timers must be available to allow for correct dwell time and to minimize treatment errors. During a gamma radiation procedure, additional sterile gowns and gloves should be open on a table in the treatment room for cases of emergency when staff members need to approach the patient rapidly.

Angiography

Terminology

As brachytherapy involves complex mechanisms of action and detailed angiographic assessment, some familiarity with terminology is helpful.

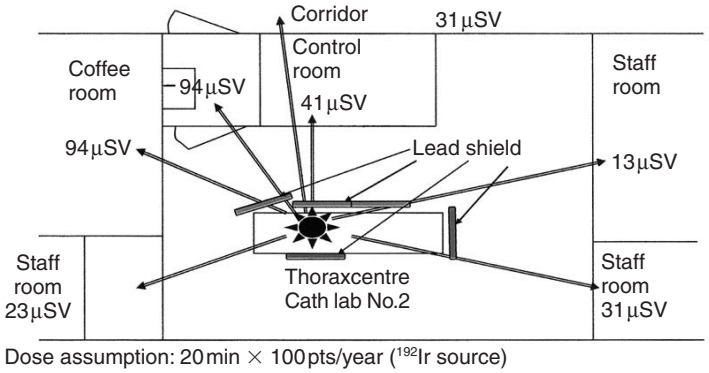

Figure 15.6
Example dose calculation in the catheterization laboratory and the adjacent rooms. Dose calculation is given as cumulative dose per year for an ^{192}Ir source with an activity of 18 GBq under the assumption that 100 patients would be treated for 20 min each. The walls of the catheterization laboratory do have a shielding of an equivalent of 6 mm lead. Additional mobile shielding with 25 mm lead is positioned around the patient.

- The **vessel segment** is the coronary segment bordered by angiographically visible side-branches which encompass the original lesion, all angioplasty devices and the radiation source (Fig. 15.7).
- The **target segment** is defined by the proximal and distal margin of the obstructed segment (see Fig. 15.7).
- The macroscopic **injured segment** is defined as the segment encompassed by the most proximal and most distal position of the angioplasty device (e.g. rotablator burr), or marker of the angioplasty balloon, and all visible vessel injury as assessed by fluoroscopy (Fig. 15.8).
- The **irradiated segment** is defined as the segment encompassed by the inner edge of the radiopaque markers of the source train or the length of the radioactive stent (Fig. 15.9). It is of note, that the effective irradiated segment, which receives full prescribed therapeutic radiation dose (>90% isodose rate), is slightly shorter as a result of the dose fall-off caused by the limited size of the source train. The exact delineation of the effective irradiated segment is complicated, as it requires the knowledge of the individual dose profiles for each isotope and source design (Fig. 15.10)
- **Edge segments** are the vessel segments at the extremities of the radiation source (catheter-based source, radioactive stent or balloon), which do not receive the full therapeutic radiation dose. The length of the edge segments is dependent on the isodose profile of the individual source (Fig. 15.11).
- In coronary brachytherapy, **geographic miss** is defined as a mismatch between injured and irradiated segments: it occurs when the injured segment is not completely covered by the irradiated segment (Fig. 15.12).

General requirements

Angiography should be done in biplane views. At the start of the procedure, two projections are selected with more than 30° difference in rotation. Foreshortening and side branch overlapping should be avoided. The meticulous documentation of all angioplasty devices and the radiation source in place with contrast medium, using the same projections, is essential. Inadequate angiographic documentation, which hampers identification of irradiated and injured segments, is seen in up to 50% of cases enrolled in brachytherapy trials.

Primary angiography

Primary angiography identifies the culprit lesion, the 'target segment' and the 'vessel segment'. Basic considerations are:

- Vessel size (dose prescription, radioactive stent selection);
- Lesion accessibility for the source (dimensions, stiffness);
- Lesion position (ostial lesions virtually all have geographic miss, as source positioning with a proximal safety margin is not possible);
- Strategy of angioplasty prior to radiation;
- Lesion length (length of source required to cover complete injured segment);
- Side branches (in bifurcation lesions, only one side branch can receive radiation).

Primary angiography also assists in deciding the 'best projection' for documenting the complete procedure. Eventually necessary additional shielding (from gamma radiation) has to be considered. The image intensifier has to be positioned in such a way that the lead shielding can be placed closely to the patient.

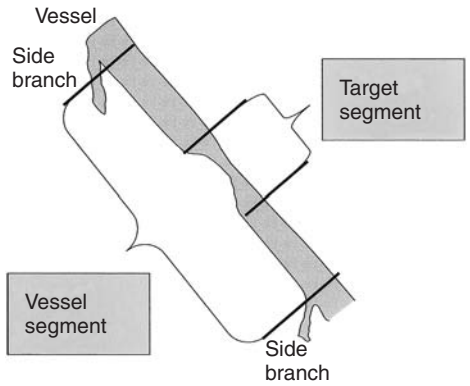

Figure 15.7

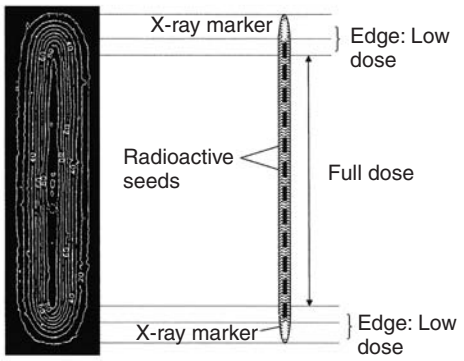

Figure 15.10

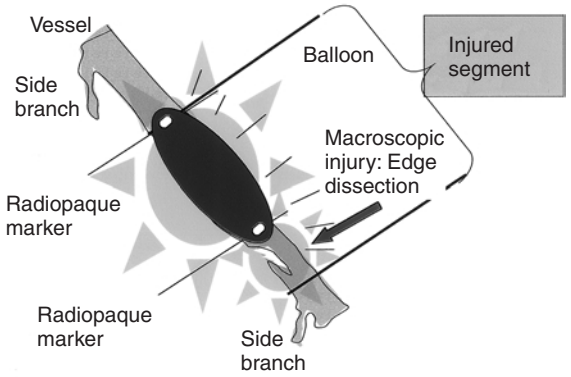

Figure 15.8

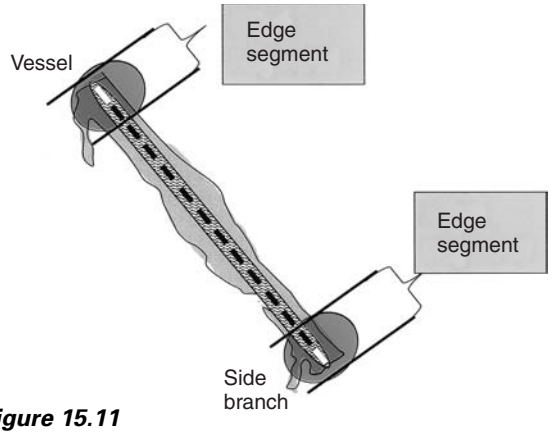

Figure 15.11

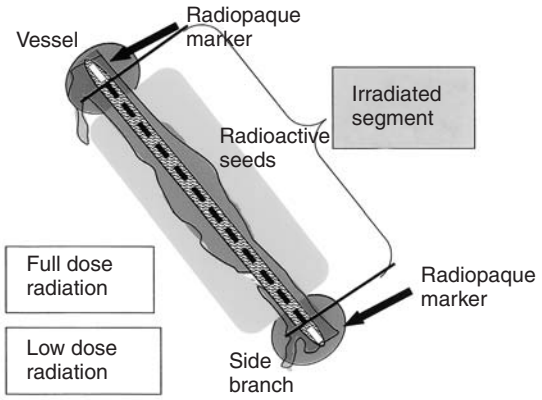

Figure 15.9

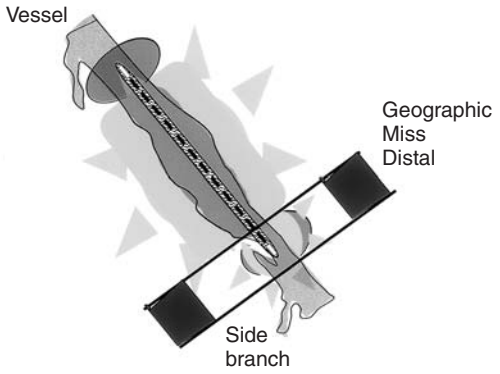

Figure 15.12

Figures 15.7–15.12
Angiography terminology.

Angioplasty

Prior angioplasty might consist of debulking (by directional or rotational atherectomy or laser), stent implantation or 'simple' balloon inflation and is performed in the conventional way. It is important that angioplasty is not stopped before reaching a satisfactory result. Every instrumentation after radiation therapy carries the risk of geographic miss.

Dose prescription and source selection

The treated coronary artery is usually 2.0–5.0 cm in length, with a diameter of 3.0–5.0 mm and a vessel wall thickness of 0.5–3.0 mm. The radiation dose given to the vessel wall should probably target the media as well as the adventitia and is delivered at 0.5–5.0 mm the long axis of the source. Dose prescription and source selection are performed in close collaboration with the radiation oncologist.

Given the radioactivity and dose rate of the selected source, dwell time is dependent on the vessel size.

The length of the source should be selected in such a way, that:

- The vessel segment which has been 'touched' by any angioplasty device is completely covered;
- The vessel segment which shows macroscopic injury is also completely covered;
- There is sufficient safety margin at the proximal and distal end of the source to guarantee full dose radiation of the treated segment.

It is recommended that the length of a source train includes a 'safety margin' of 1 seed outside the injured segment at each end (Figs 15.13 and 15.14). An example of geographic miss, caused by selection of an inappropriate, too short source is given in Fig. 15.15.

Radiation

The radiation oncologist prepares the brachytherapy device. Meanwhile it is helpful for the operator to review the angiograms. This allows for a precise image of the 'injured segment' relative to landmarks such as side-branches. If gamma radiation is used, lead shielding devices must be installed.

The guiding catheter should be correctly positioned at the coronary ostium: if it is too deep, it will obstruct flow and may creep further into the coronary artery during the pro-

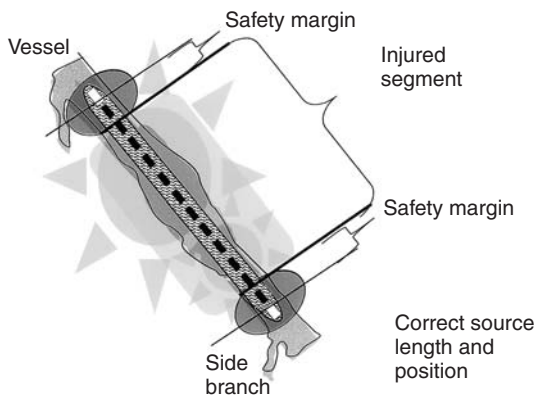

Figure 15.13
Correct source length and source position. The source is able to cover the injured area as indicated by the balloon markers and the area with macroscopic vessel injury by full-dose radiation. Proximal and distal there is a safety margin of 1 seed.

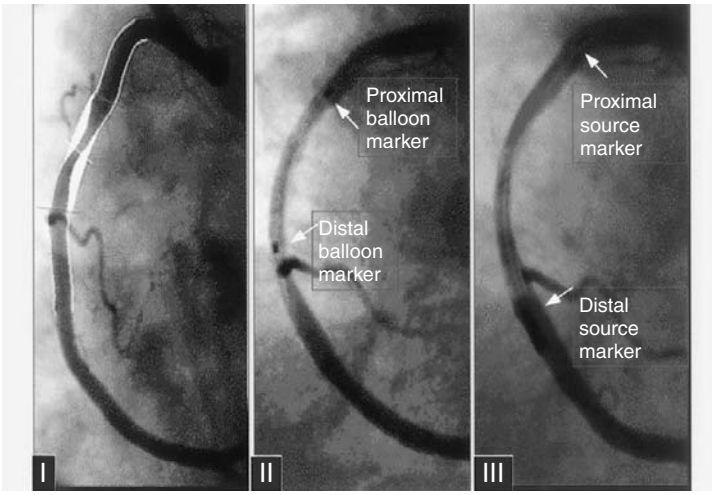

Figure 15.14
Correct source length and source position. Angiogram of an in-stent restenosis in a right coronary artery. The white lines indicate the lesion as given by quantitative coronary analysis (I). Treatment by balloon angioplasty: the position of the balloon is documented by injection of radioque contrast medium, which reveals the radio-opaque markers at the extremities of the balloon (II). The injured area is completely covered by the source ($^{90}Sr/^{90}Y$ system) (III).

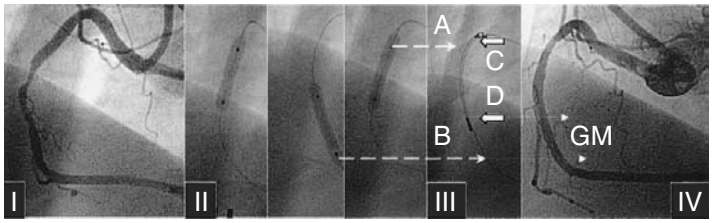

Figure 15.15
Geographic miss during treatment of an in-stent restenosis in a right coronary artery (I). The position of the angioplasty balloons is documented at maximum inflation (II). Positioning of the source with radio-opaque markers at the proximal (C) and at the distal (D) end ($^{90}Sr/^{90}Y$ system) (III). Line A indicates the most proximal balloon position, line B indicates the most distal balloon position within the coronary. The source (C–D) is too short to cover the injured area (A–B), so causing distal geographic miss (GM) (IV).

cedure; if it is too far away, it may slip during the procedure and move the source ribbon. Then the catheter which accommodates the dummy source is carefully advanced into the vessel. Most radiation delivery catheter are fragile without inserted ribbon and may easily kink during insertion. If stented lesions are treated, care is required, particularly in tortuous vessels where the catheter may become caught on the stent struts.

An angiogram with the dummy source in place should be done. If angiography confirms correct positioning, with complete coverage of the injured segment and safety margins, the radiation oncologist removes the dummy source, connects the afterloader device to the catheter and delivers the source. Some systems may require withdrawal of the guidewire. The radioactive source must be filmed in place with contrast medium, repeating the projections used for angioplasty. Care should be taken to not over-tighten the O-ring and Y-connector while attempting to obtain good quality contrast injections, as this may crimp the source ribbon and obstruct movement. During radiation delivery, all non-essential personnel must leave the procedure room.

At the end of the dwell time, the radiation oncologist removes the source. In the case of long dwell times (10–20 min), to avoid thrombotic embolization after withdrawal of the source, the contrast medium should be withdrawn into the delivery syringe prior to injection down the coronary artery. While removing the delivery catheter, care should be taken not to push the guide too far distally into the vessel. A final angiogram should confirm a good angioplasty result and the absence of dissections and/or thrombus.

Postprocedural care

The arterial sheath is withdrawn immediately after the procedure and the access site sealed with a closure device. In case of a difficult arterial puncture with substantial fibrosis, the sheath is removed 6 hours after the procedure and the artery manually compressed. All patients must receive effective antiplatelet therapy for at least 6 months. Aspirin should be prescribed indefinitely in combination with ticlopidine (250 mg twice a day), or clopidogrel (75 mg daily) for 12 months. This is essential to avoid late thrombotic occlusion, which has been observed with an incidence of up to 9.2% in the early phase of catheter-based brachytherapy (Fig. 15.16), most probably because of delay in endothelialization which might increase the chance of subacute thrombosis.

Complications

Procedural complications

Procedural complications include all complications typically linked to the angioplasty/debulking procedure. When using radioactive stents, all complications typical for conventional stenting have to be taken into account. Most complications related to brachytherapy by removable sources are caused by the relatively high profile and stiffness of the delivery catheter:

- Myocardial ischemia with angina and/or ECG changes, which might necessitate fractionation (i.e. interruption of the radiation

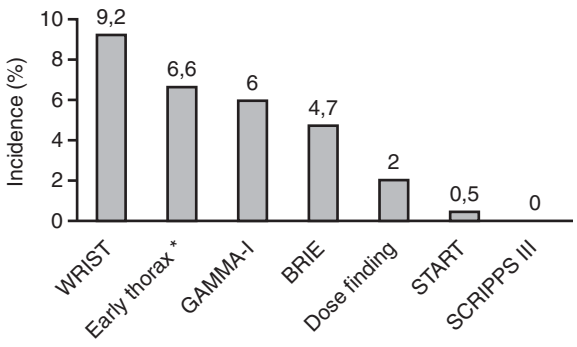

Figure 15.16
Incidence of late thrombotic vessel occlusion after catheter-based brachytherapy.

and delivery of radiation during two dwell times) of the dose (approximately 4% of the patients);
- Dissection after manipulation of the delivery catheter (approximately 10% of lesions).

Furthermore, radiation increases local thrombogenicity, which promotes intracoronary thrombus formation during active treatment (approximately 4% of lesions). In these cases, GP IIb/IIIa inhibitors should be given deliberately.

Procedural emergencies

Catheter-based line sources

Prolonged retrieval represents one of the most serious technical events which can produce unwanted dose to the patient and staff. In that first case, the entire treatment catheter should be withdrawn and placed into the bail-out box. If that is not successful, an attempt should be made to move the source into a larger diameter artery whilst calling for emergency surgery.

Balloon-based fluid or gaseous sources

Radioactive fluid-filled balloons might leak or burst and spill their contents into the patient's blood stream. The radioactive material must be physiologically cleared from the patient before an unacceptable dose is delivered to any tissue. In this instance, gaseous 133Xe is rapidly exhaled and presents minimum radiation hazard to the patient.

In all cases of emergency, the physicist's responsibility is to remain focused on safely retrieving the sources and minimizing unnecessary exposure of patients and staff. To allow for rapid and well-directed action, contingency plans must be made in advance, discussed and rehearsed for a variety of likely and unlikely occurrences.

Logistics and regulatory considerations

For transportation, storage and handling of nuclear sources, European countries require various licenses according to individual nuclear laws. In general, the institute or hospital needs a license for using radioactive material. Within the institute or hospital, a local permission must be obtained which is mostly linked to specific room conditions and expertise of the personnel. Mandatory key personnel include a radiation oncologist, a medical physicist, a radiation safety officer and a cardiologist. Clinical responsibility lies with the radiation oncologist, though he may delegate practical aspects to others. In the USA, the Nuclear Regulatory Commission (www.nrc.gov) regulates radiation safety. Medical issues are addressed under a section of Federal law referred to as CFR Part 35 ('*Staff requirements: SECY-99-201-Draft Final Rule-10 CFR, Part 35,* ''Medical use of byproduct material''. February 16, 2000.').

Radiation protection and safety considerations

In Europe, standards for the protection of patients, health workers and the public against exposure to radiation have been specified in two directives (96/29/Euratom;[31] 97/3/Euratom[32]) and are now being incorporated into national laws. Radiation protection is determined by two principles: exposure must be justified by showing that it confers more benefit than detriment and exposure

should be as low as reasonably achievable to deliver that benefit.

Source

Every source must be inspected on receipt, which involves visual inspection of the shielding, calibration to verify the exact level of activity and, in line sources, checking the number and activity of sources. Sources must be stored securely and held under lock and key. The time necessary to transfer the source in a shielded delivery device ('pig') to the laboratory must be taken into account by treatment protocols.

The storing facilities must provide sufficient shielding not only for the gamma sources (^{192}Ir), but also for the beta sources (^{90}Sr/^{90}Y and ^{32}P), that produce significant bremstrahlung. ^{32}P has a half-life of 14 days only. In consequence, ^{32}P sources have to be exchanged every two weeks. ^{90}Sr/^{90}Y sources require a yearly check, especially for the mechanical condition of the source.

The shielding device used to transport the source can itself be a source of radiation. The operator's dose can be reduced by not touching the shielding device. During delivery into the coronary artery and retrieval, the source is unshielded for a few seconds. Again, the operator's dose is reduced by not touching the treatment catheter and keeping distance. Direct manual contact with a high dose rate source is hazardous. During treatment with gamma radiation, with the exception of the radiation oncologist, all personnel must leave the procedure room in order to limit their exposure to radiation.

Catheterization laboratory design and equipment

Actual shielding requirements are specific to the catheterization laboratory, depending on the size and configuration of the procedure room and adjacent rooms. Principally, when working with gamma radiation, special shielding (minimum thickness 25 mm lead) is required in the procedure room to block the gamma rays (e.g. mobile shields of approximately 200 kg positioned close to the patient). The control room must be protected by a mobile lead shield. Outside the procedure room, the level of exposure must be estimated and regularly monitored in adjacent rooms. Beta radiation requires no specific shielding of the procedure room or of adjacent rooms.

Patient safety

Principal risks

Principal risks related to intracoronary radiation include:

- Damage to the artery wall with consecutive perforation and/or aneurysm formation. This risk seems to be dose related (>30 Gy) and low.
- Accelerated coronary artery disease is a known side-effect of high-dose radiation (>35 Gy) for the treatment of neoplasms. Intermediate doses (30–40 Gy) have shown a low risk of cardiac disease during longterm follow-up.
- Radiation-induced carcinogenesis. This risk appears to be low, at least in beta radiation, as the dose beyond the immediate target lesion is low and the exposed tissues (e.g., arteries, veins, cardiac muscle, and

pericardium) have a low spontaneous carcinogenicity rate.

Technical risk

The main technical risk related to intracoronary radiation is the failure to deploy and retrieve the source smoothly. Therefore, proper source passage into the target coronary artery should be routinely tested by deploying and retrieving a dummy source. A dummy source allows also for control of the treatment position within the coronary artery and repositioning of the delivery catheter if necessary.

Limitations

Besides the wanted inhibition of neointima proliferation, radiation can potentially be associated with unwanted acute, mid- and longterm effects. While acute unwanted effects, such as increment of local thrombogenicity are well known, there are few preclinical or clinical data on the longterm consequences of radiation exposure of coronary arteries. It may take many years for unwanted effects to become manifest.

Important issues regarding the midterm outcome (6 months) seem to be low-dose radiation exposure to tissue at the edges of the source and delayed healing. Low radiation doses (4–8 Gy) may stimulate neointimal proliferation.[33,34] This could be because growth factors are synthesized de novo and secreted by surviving cells. These growth factors might promote the proliferation of smooth muscle cells.

Geographic miss, where the injured area is not completely covered by full-dose radiation, is a major cause for edge restenosis.[28] The incidence of geographic miss ranges from 18% to 34%. In case of geographic miss, a restenosis rate of 39% was seen, versus 9% when there was no geographic miss. Delayed wound healing with persistent dissections after beta radiation have been observed at 6-month angiographic follow-up and might be a possible cause of late thrombotic vessel occlusion or delayed restenosis as seen in the Condado, SCRIPPS and WRIST trials.[3,4,6]

The longterm course after radiation might be complicated by aneurysm formation, accelerated atherosclerosis and late fibrosis. Delayed depletion of some cells (adventitial cells) could lead to subsequent repopulation, whereby smooth muscle cells from the media could be replaced progressively by fibroblasts and extracellular matrix. This leads to fibrosis, as has been described in animal experiments. Whether these findings are relevant to clinical practice is unclear.

Truly longterm follow-up data are limited to case series.[35–37] The longest follow-up is reported by Liermann in 40 patients at 7.5 years after radiation therapy (^{192}Ir) for in-stent restenosis in peripheral arteries.[38] The longest follow-up after radiation in coronary arteries is provided by the Condado series of 21 patients.[3] However, these studies were uncontrolled investigations. A follow-up of 3 years is available from the randomized SCRIPPS trial.[4] The target lesion revascularization rate remained significantly lower at 3 years for patients in the treatment arm (^{192}Ir for in-stent restenosis).[39] However, evidence on longterm effects in humans can only be generated by evaluation of sufficient numbers of patients over several years.

Safety data are only available for the combination of radiation therapy with stainless steel stents. There are no data available on the simultaneous or sequential application of

radiation and new, upcoming drug-eluting stents. However, interaction of radiation and drugs suggested for local delivery by coated stents (e.g. actinomycin-D, paclitaxel) on the cellular level has been described.[40–43] While synergistic effects are used in cancer therapy, the possible consequences in the setting of coronary artery disease and restenosis are unknown. Therefore, any combination of these two treatment principles should be avoided.

Future directions

Endovascular radiotherapy has been demonstrated to be safe and feasible over a short-and mid-term perspective. There are questions which remain to be answered before determining the potential of this new technique. First, the use of beta- or gamma-sources or a combination of both. Second, the use of centering or non-centering devices. Further, to determine the best vehicle for radiation: solid (wire or seed train), liquid (filled balloon) or gaseous. Finally, the target tissue must be defined as well as the minimal effective dose to be delivered. Ongoing trials in Europe and in the USA address many of these issues and their findings are eagerly awaited.

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16

Syndrome X

Richard Cooke

Introduction

The number of patients investigated by coronary angiography each year in the UK is 1600 per million.[1] The figure is less than in other European countries and in the USA where as many as 4000 per million people are investigated each year. The proportion of patients in whom the angiogram is normal and shows no significant stenoses is overall 15–20% (Table 16.1), but this hides important sex differences. The incidence of normal coronary angiogram is less in men, around 13%, and as high as 55% in women.[2,3] The explanation of this difference is uncertain. It is likely that the greater incidence of normal tests reflects a failure to take into account prior probability and risk factors before listing for angiography.[4]

It is important not to ignore the significant number of patients with similar symptoms, but in whom angiography is not performed. The group in whom investigation by coronary angiography is carried out merely comprises the tip of the iceberg.[5] What is it that sets these apart from the rest and causes refusal to accept that the cause of pain is in most cases non-cardiac, most likely functional? One reason is a reluctance to acknowledge that patients who were thought, prior to listing for coronary angiography, to have angina do not have a cardiac explanation for their symptoms. Indeed many have risk factors for vascular disease not dissimilar to patients with angiographically confirmed coronary disease.[6] If the coronary angiogram is normal, so the reasoning goes, it is the test which is at fault and only time and the development of more sophisticated technology will identify the cardiac abnormality. Such reasoning is ill-founded; despite numerous various attempts to identify a cardiac cause in these patients since the 1970s none has been found.

A further, more significant reason for the interest in this group is that, despite the reassurance of a normal coronary angiogram, many patients continue to report symptoms and remain functionally impaired.[7] These patients represent a major challenge for management, and often become chronic attenders at outpatient clinics, either in hospital or in primary care (Table 16.2).

Terminology

The term 'syndrome X' was first used in 1973 by Kemp in an editorial which describe the so-called paradox of normal coronary angiogram and chest pain resembling angina.[8] This paradox was first reported by Likoff et al in 1967.[9] It was recognized that, in many cases, the chest pain was atypical of angina and not

	Patients	% NCA (near normal)	% NCA (normal)
NORTH AMERICA			
Marchandise et al 1978[69]	8630	33%	23%
Pastermak et al 1980[70]	3242	5%	4%
Faxon et al 1982[71]	379	19%	
Papanicolaou et al 1986[52]	7317	27%	
Kemp et al 1986[72]	21 487	19%	15%
Phibbs et al 1988[73] (4 centers)	1160	17%	
	1061	16%	
	291	9%	
	911	8%	
Dans et al 1988[74] (2 centers)	201	13%	10%
	247	24%	20%
McCroskery et al 1991[75]	115	24%	
Morise et al 1993[11]	8000	25%	
EUROPE			
Favaro et al 1987[76]	174	18%	
Nevens et al 1991[77]	1761	14%	
DeCaestecker et al 1991[58]	1374	NA	6%
Tweddel et al 1992[36]	3150	10%	
Juelsgaard et al 1993[57]	990	9%	
Gray et al 1994[78] (3 centers)	150	18%	
	371	12%	
	154	14%	

Table 16.1
Incidence of normal, or near normal, coronary angiograms.

every patient had an abnormal exercise stress ECG, which is now often said to form part of the paradox.

Some patients with normal coronary angiograms will have chest pain symptoms which more closely resemble angina than others but these are few and far between. Day and Sowton in 1976 observed that, in most cases, the chest pain was inconsistently related to physical exercise, occurred frequently at rest, and tended to last longer than the 5 minutes typical of angina.[10] These observations were confirmed in a more systematic appraisal by Cooke et al.[6] In this study, the chest pain symptoms were recorded immediately prior to performing coronary angiography and a comparison made between those patients with normal studies and those whose angina was confirmed by the demonstration of significant stenoses. There was little to distin-

	Follow-up (years)	Patients	No (%) taking anti-anginal drugs
Bass et al 1983[79]	1.0	46	26 (56%)
Isner et al 1981[80]	4.3	118	75 (64%)
Kemp et al 1973[8]	3.0	200	80 (40%)
Bemiller et al 1973[81]	4.1	37	28 (75%)
Day and Sowton 1976[10]	2.0	45	11 (25%)
Okene et al 1980[82]	1.3	57	14 (25%)
Faxon et al 1982[72]	2.0	72	44 (61%)
Papanicolaou et al 1986[52]	6.3	1361	375 (27%)
Lantinga et al 1988[83]	1.3	24	19 (79%)
Pasternak et al 1980[70]	3.5	159	74 (46%)
Chauhan et al 1993[13]	3.0	82	45 (55%)

Table 16.2
Number of patients continuing to take anti-anginal medication after a normal coronary angiogram.

guish the groups in terms of quality, location and radiation of pain which might be explained by selection, since patients who have pain atypical in this respect are unlikely to be listed for invasive investigations. There were important differences however in the consistency of provocation of pain by exercise or stress, the duration of pain, and the frequency of rest pain.

Similarly, Morise et al, reported that only 4% of patients (4 out of 109) studied over a 10-year period had symptoms that were typical of angina where the coronary angiogram was normal.[11] A higher proportion had abnormal stress ECGs (25 out of 109), but these had atypical chest pain symptoms. Kaski et al made the same observation on a series of 90 patients referred to a specialist chest pain clinic designed to investigate syndrome X.[12] Chauhan et al reported that many patients present with unstable symptoms and are admitted as emergency cases.[13] This is likely to be a reflection of the frequency of atypical rest pain and the natural reluctance to discharge or to investigate non-invasively patients who may have rest angina.

There is a view that the approach to managing patients with physical symptoms and no identifiable cause is complicated by often unhelpful and controversial terminology and disease concepts.[14] Patients who present with chest pain and normal coronary angiography share an overlap in symptomatology with other patients who present to different specialities. They present with clusters of chronically medically unexplained symptoms and are given labels such as irritable bowel syndrome, chronic fatigue syndrome or fibromyalgia. The term 'psychosomatic illness' is no longer in favor and is considered unhelpful. It may be considered offensive to the patient and misleading in that it implies that the symptoms

are all in the mind. The term 'somatization disorder' is used to describe the process where people experience and communicate psychological distress as physical symptoms, some of which may be a misinterpretation of normal physiological bodily function or due to minor physical abnormalities.[15] However, the use of the term 'medically unexplained' symptoms or chest pain is preferred, since it makes no statements about causation of symptoms, describes the clinical situation, and is neutral as far as patients are concerned.

The term 'syndrome X' is also used to describe a metabolic syndrome, first reported by Reaven et al in 1988. This refers to the association of impaired glucose tolerance, insulin resistance, and hypertension (see Chapter 6).[16] Some patients with chest pain and normal coronary angiography may have this cluster of risk factors, but this is a separate syndrome.

Arterial disease

The first question asked is whether a significant coronary stenosis may have been missed at angiography. This possibly was of more concern in the early days before the value of multiple angulated views was appreciated and the imaging technology less advanced.[17] It would now be unusual to miss a significant lesion angiographically, although caution is needed in assessing ostial lesions where a small diagnostic catheter may pass through the stenosis and obscure the presence of a lesion. In cases where there is a truly typical history of angina, a thallium perfusion study may be useful. In one case showing extensive reversible anterior ischemia this was markedly abnormal. The angiogram was repeated and showed complete occlusion of the LAD artery which, 6 months' previously was reported as normal.[18] Such cases are unusual.

Erbel and Ge reported their experience of intravascular cardiac ultrasound in 1996.[19] In 44 patients with angiographically normal coronary arteries, the LAD and left main stems were examined. In 21 of these (48%), there was evidence of coronary atheroma and plaque disease. There were however no significant obstructive epicardial lesions. The observation of atheroma is not surprising, since patients selected for coronary angiography often have risk factors for coronary atheroma. These are correctly and frequently used as part of the decision-making process when deciding to investigate chest pain further. Shemesh et al studied 81 consecutive women listed for coronary angiography. Double helical computed tomography (CT) was used to detect coronary calcification.[20] In 10 out of 16 patients (63%) with normal coronary angiograms and abnormal exercise ECGs, the syndrome X group, there was significant calcification. This compared with a prevalence of 45 out of 47 (96%) in patients with angiographically confirmed disease, and of 18 (22%) patients who had normal exercise tests. The presence of atheroma however by no means establishes this as the cause of pain where there is no demonstrable obstruction to blood flow or evidence of myocardial ischemia.

Investigators have taken this further and examined the responses of the epicardial coronary arteries to vasodilators, both via and independently of the endothelial system. Vrints et al measured the left epicardial coronary arterial diameters in response to acetylcholine, an endothelium-dependent vasodilator in patients with normal coronary angiograms.[21] In controls, 12 patients whose

chest pain was atypical, the normal expected vasodilator response occurred. By comparison, in the 12 study patients whose pain was typical of angina, the coronary arteries constricted and many of these developed chest pain and ECG changes during the infusion.

Egashira et al studied nine patients with syndrome X and 10 controls with non-cardiac chest pain.[22] In contrast to the study of Vrints et al, patients with risk factors for vascular disease, principally raised cholesterol, high blood pressure and hence endothelial dysfunction, were excluded. Not surprisingly, no evidence of endothelial dysfunction was found and the epicardial arteries dilated normally in response to the acetylcholine infusion. A curious observation, however, was that the coronary flow reserve, which reflected the response of the coronary microvasculature, was significantly less in the patient group than in controls. Chauhan et al also found reduced coronary flow reserve in response to acetylcholine infusion but, in their study, the responses were also abnormal using papaverine, an endothelial independent vasodilator.[23] In contrast, Holdright et al found normal coronary flow reserve in response to both acetylcholine and papaverine.[24,25] The literature is therefore inconsistent and confusing.

There is no pathologic evidence of small vessel coronary disease, and it is well recognized and accepted that intramyocardial blood vessels are immune from atheroma. Shirey performed percutaneous punch biopsies of the heart and found no evidence of microvascular disease in 14 patients with normal coronary angiograms and normal left ventricular function.[26] Opherk et al[27] and Richardson et al[28] used endomyocardial biopsies and also found no evidence of small vessel disease. Suzuki et al, however, reported significant arteriosclerosis of the small vessels caused principally by medial thickening in 18 of 19 syndrome X patients.[29] Similar changes were present in only one of 10 controls who had atypical chest pain. In view of the small numbers in the study, and the wide variation in appearances of normal hearts, these observations should be treated with some caution.

What then of the functional responses of the small coronary vessels? These have been tested, using thermodilution catheters in the coronary sinus and, more recently, intracoronary ultrasound. Both these tests are invasive and a major limitation has been an inability to test the responses in large numbers of healthy volunteers. The studies have therefore been confined to comparisons of various subgroups of patients separated by a variety of clinical features, including chest pain characteristics considered cardiac or non-cardiac, reproduction of chest pain by atrial pacing, abnormal exercise ECG test or abnormal single photon scintigraphy.[30–32] Often significant differences were reported between these groups, although the studies are noteworthy for the considerable overlap and large standard deviation of results. Some positive publication bias is possible in view of the small numbers of patients studied.

There is likely to be a wide variation in blood flow responses in the normal population. Thus studies using positron emission tomography to quantify blood flow have shown no significant differences between patients with syndrome X and healthy volunteers.[33,34] A further confounding issue when measuring coronary blood flow is the reliance on comparisons of flow at resting basal metabolic state and flow when the microvasculature is maximally dilated. In many studies, the basal flow is not quantified and the coronary

flow reserve merely expressed as a ratio. This is completely unsatisfactory since the basal flow may be increased in the study group to account for the reduced flow reserve ratio. Gallassi et al reported a significantly lower flow reserve in the patient group compared to controls (2.4 vs 3.9), but the differences were due to a higher basal flow in the patient group and there were no differences in absolute blood flow at peak stress.[35]

Myocardial ischemia

It is generally, although not universally, accepted that, for a blood flow abnormality to cause chest pain, there must be some evidence of myocardial ischemia. ST segment depression during exercise testing is not in itself sufficient evidence of ischemia, since other things may cause this. Moreover ischemia may be present where there is no ST depression. The finding is therefore non-specific and lacks sensitivity. Efforts to establish myocardial ischemia by other investigative methods have generally been unsuccessful. The ischemic cascade (Fig. 16.1) shows the various stages as ischemia manifests itself when the heart is stressed.

Regional flow heterogeneity is one of the earliest signs of ischemia. Tweddell et al reported a high incidence of regional perfusion abnormalities using thallium scintigraphy in a consecutive series of patients investigated in Glasgow for chest pain and found to have normal coronary angiography.[36] The study however only used planar imaging and reversibility was not assessed by reimaging. The incidence of defects is also likely to be a gross overestimate since the study came from a unit where an abnormal scan was a prerequisite to listing for coronary angiography, hence selection bias. Rosano et al reported reversible perfusion abnormalities in only 4 of 24 (17%) patients with syndrome X, after excluding patients with hypertension, previous infarction, valve disease and cardiomyopathy.[37] In an unreported study, Technetium Sesta Mibi rest and exercise stress studies were performed in a consecutive series of 64 patients with normal coronary angiograms. None had previously been investigated by nuclear imaging and pretest selection bias was therefore elimi-

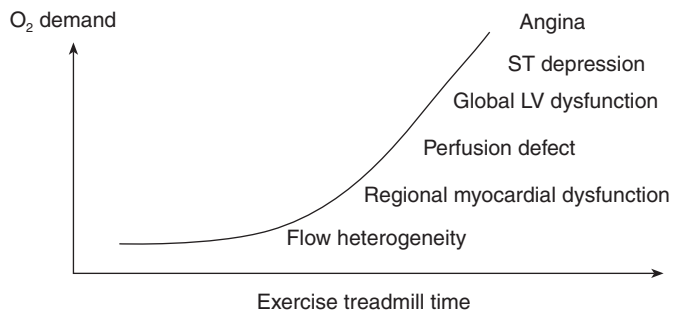

Figure 16.1
Ischemic cascade.

nated. All had completely normal coronary angiograms, normal echocardiograms, normal resting ECGs and no history of myocardial infarction. In approximately a third of cases significant reversible defects were reported, but in most cases the defects were minor.[38] There was no difference in the incidence of abnormalities, depending on whether the chest pain was typical or atypical, or whether there was ST segment depression or not on the exercise ECG.

Regional perfusion abnormalities during single photon scintigraphy may represent genuine abnormalities of flow that reflect myocardial ischemia, presumably caused by abnormalities of the small vessels. The technique, however, is prone to technical error, often as a result of attenuation. Positron emission tomography (PET) studies avoid the problem of tissue attenuation, and have failed to show regional flow abnormalities in syndrome X patients.[33,34,39] A greater heterogeneity of flow compared to controls was found by Galassi et al, though this involved statistical analysis following arbitrary division of the myocardium into small (<2.5 cm^3) regions of interest.[35] There is no biologic foundation to this approach and, as with the other PET studies, no regional abnormalities of flow were detected.

One of the early metabolic markers of ischemia is the production of lactate.[40,41] This has been used clinically as a marker of ischemia and involves sampling from the coronary sinus to compare levels to those in the arterial blood before and after stress. The concentrations involved may be small, which means that sampling and other technical errors may lead to spurious results. Only the net production of lactate is said to indicate ischemia. Table 16.3 shows the incidence of abnormalities in reported studies and shows the large degree of variability. It is also remarkable that the highest incidence of abnormalities is reported in older studies carried out before 1990, where patients may

		Patients	*No (%) lactate producers*
Arbogast and Bourassa 1973[84]		10	3 (30%)
Kemp et al 1973[8]		100	22 (22%)
Mammohansingh and Parker 1975[85]		16	2 (13%)
Jackson et al 1978[41]		25	0
Greenberg et al 1987[86]		27	10 (37%)
Cannon et al 1992[87]	Gp1	141	14 (20%)
	Gp2	59	0
Camici et al 1991[30]	Gp1	12	0
	Gp2	10	0
Suzuki et al 1994[29]		21	0

Table 16.3
Lactate production in patients with normal coronary angiograms.

not have been well selected to exclude such confounding factors as hypertension and diabetes mellitus.

Rosano et al performed continuous monitoring of coronary sinus pH and also evaluated oxygen saturation during atrial pacing in 14 patients with chest pain and normal coronary angiograms.[42] Many had abnormal exercise ECG tests and perfusion abnormalities on thallium scintigraphy. The results were compared to controls with angiographically confirmed stenoses and angina. Nearly all developed severe chest pain during the study but only three patients with chest pain and normal angiograms had a drop in the coronary sinus pH >0.02 pH units and in oxygen saturation >8% consistent with myocardial ischemia. These results are similar to an earlier study by Crake et al which reported a fall in coronary sinsus oxygen saturation during atrial pacing in only 2 of 10 patients with syndrome X.[43]

Abnormal left ventricular wall motion during stress echocardiography in patients with normal coronary angiograms is unusual. Picano et al,[44] in a study of 19 patients using dipyridamole as the stressor, and Nihoyannopoulos et al,[45] using exercise stress in 18 patients, reported no abnormalities despite the occurrence of significant ST segment depression and chest pain in the majority of cases. Cannon et al also reported no wall motion abnormalities using dobutamine stress and transesophageal imaging. In this study, the coronary vasomotor responses to acetylcholine were measured in 42 patients with normal angiograms and chest pain.[46] There were no differences in the responses in coronary artery diameters or blood flow between the 12 patients whose exercise stress ECG was abnormal compared to the rest of the group, or in the degree of left ventricular wall thickening in response to dobutamine. Furthermore, patients whose blood flow responses were in the lowest quartile had similar wall motion responses compared to those in the highest quartile.

The absence of wall motion abnormalities does not exclude myocardial ischemia, which is either patchy or confined to the subendocardium. Henein et al reported abnormalities of left and right ventricular long axis which shortened at rest in 70% of syndrome X patients and in only 5% of controls.[47] The hypothesis is that the long axis function is mainly supported by subendocardial fibers, which are particularly susceptible to ischemia. This is a method of evaluation which is not widely used and impossible to validate as there is no gold standard for subendocardial ischemia. There was no correlation of abnormalities of long axis function with other markers of ischemia, such as reversible perfusion abnormalities during single photon scintigraphy.

Levy et al measured pulmonary artery diastolic pressure, a marker of left ventricular end diastolic pressure, during treadmill exercise and ambulatory monitoring using a catheter-mounted transducer.[48] In patients with significant stenoses at angiography, ST segment depression during ambulatory monitoring was invariably associated with a rise in pressure. In patients with normal angiograms, however, ST segment changes were not associated with any elevations. During treadmill exercise the pulmonary artery pressure rose in 2 of 6 patients with normal coronary angiograms and ST depression, but in each case the rise was small and of similar magnitude to that observed in normal controls.

In contrast to these studies, which show

		Patients	Global	Regional	Total
Borer et al 1979[88]		21	0	0	0
Berger et al 1981[89]		31	12 (39%)	4 (13%)	–
Gibbons et al 1981[90]		60	27 (45%)	4 (7%)	–
Osbakken et al 1983[91]		21	8 (38%)	–	8 (38%)
Rozanski et al 1983[92]		45	23 (51%)	29 (64%)	–
Legrand et al 1985[32]		18	5 (28%)	4 (22%)	–
Cannon et al 1985[93]		26	18 (69%)	12 (46%)	–
Favaro et al 1987[76]		32	22 (69%)	12 (37%)	–
Camici et al 1991[30]		12	0	0	0
Cannon et al 1992[87]	Gp1	136	–	–	56 (41%)
	Gp2	56	–	–	7 (13%)
Taki et al 1994[94]		14	11 (79%)	–	11 (79%)
Cannon et al 1994[68]		49	–	–	11 (22%)

Table 16.4
Left ventricular dysfunction in patients with normal coronary angiograms: radionuclide studies.

little evidence of ischemic left ventricular dysfunction in the absence of angiographic stenoses, reports of wall motion abnormalities using nuclear imaging are common but also very variable (Table 16.4). It may be that the assessment of wall motion with radionuclide techniques is prone to technical error because of the need to average several beats, at least in the older studies reported. A further cause of error is a reliance on the ejection fraction response to exercise, which may be quite variable depending on a number of factors, such as resting ejection fraction, end diastolic volume, workload, and the ratio of preload to afterload.

A more recent technique looking for evidence of myocardial ischemia is magnetic resonance imaging with gadolinium DTPA contrast enhancement. The paramagnetic contrast medium is given intravenously and is thought to be a sensitive marker of extracellular edema, probably ischemic in origin. Rossetti et al reported abnormal myocardial enhancement in 16 of 24 (67%) patients with syndrome X and in none of normal healthy volunteers.[49] In the majority of patients the test became normal (and the exercise ECGs also became normal) when repeated after treatment for a week with beta-blockers. The results are interesting but firm conclusions should not be made until larger numbers of healthy volunteers are studied.

Prognosis

Few patients die or have a heart attack within ten years of a normal coronary angiogram. Sand et al reported an incidence of normal coronary angiogram in 8.6% of 990 patients studied over a 7 year period.[50] Almost a third of these had abnormal exercise stress ECGs. The patients were followed up and outcomes

compared to those patients whose angiograms showed significant coronary disease. After an average follow-up period of almost 4 years, 2.4% of patients with normal coronary angiograms had died compared with 21% of patients whose angiograms were abnormal. Non-fatal myocardial infarction occurred in none, compared with 13% of patients with angiographic coronary disease. Oerlemans et al reviewed eight articles published between 1966 and 1998 concerning the prognosis of patients with suspected angina and normal coronary angiograms.[51] Per 1000 patient years, the total number of deaths ranged from 0 to 6.59, the number of deaths caused by coronary disease from 0 to 0.92 and the number of patients with non-fatal myocardial infarctions from 0 to 1.83. The figures were considered similar to those in the average population. Papanicolaou et al reported 99% 5-year, and 98% 10-year survivals in patients with normal angiograms, in a study that involved 1491 patients.[52] A fall in survival curves was noted at 5 years, which was most marked in patients with insignificant stenoses as opposed to completely normal coronary angiograms, consistent with a higher incidence of disease progression in this group.

Cox et al reviewed 139 consecutive patients with normal coronary angiograms.[53] In 101 patients, the angiogram was completely normal and showed no luminal irregularities.[53] During a 5-year follow-up period, 24 patients underwent repeat angiography because of persistent unstable symptoms. Only 2 patients had significant progression to more than 30% stenosis at angiography, both were male with minimal luminal irregularities at baseline, left bundle branch block and multiple coronary risk factors.

Patients with left bundle branch may comprise an important subgroup and have a worse prognosis than those patients whose ECG is either normal or shows ST depression. Opherk et al also followed up 40 patients with normal angiograms over four years, 14 of whom had left bundle branch block.[54] Left ventricular function was the same at baseline, but after 4 years there was a significant deterioration in patients with, but not in patients without, left bundle branch block. Romeo et al reported a similar deterioration in left ventricular function in patients with left bundle branch block over a 6-year period.[55]

Despite a good longterm prognosis with respect to freedom from death or heart attack for most patients with normal coronary angiograms, the prognosis in terms of morbidity and functional impairment remains poor and often worse than in patients with confirmed coronary disease. Sand and Juelsgaard reported that the chest pain was either unchanged or worse in 58% of patients with normal angiograms, compared with 21% of patients with coronary disease at angiography, 80% vs 64% had given up work, and 56% vs 34% had reduced daily activities.[50] The incidence of divorce was also significantly higher, at 10% vs 1%. These observations are consistent with many other previously reported trials and also with clinical experience.[56–58]

Management

Conventional antianginal treatment has often been tried before patients are investigated by coronary angiography. In view of the numerous reports of significant continuing morbidity and chest pain on follow-up in the majority of cases, one can assume that they are ineffective. Few large randomized trials however are available to confirm this. Available studies often

use surrogate endpoints in view of the small numbers of patients and these may not be relevant to clinical outcome.

Bugiardini et al in a double blind crossover placebo trial with 12 syndrome X patients reported a reduction of the number of ischemic episodes (that is ST segment depression episodes) during ambulatory ECG monitoring after propanolol but not verapamil.[59] Romeo et al reported an increase in exercise tolerance during treadmill testing with acebutolol in 15 patients with syndrome X.[60] After a mean follow-up of 5 years, however, neither acebutolol or verapamil had any important effect on symptoms.

Rogacka et al investigated the effects of trimetazidine in a study of 34 syndrome X patients.[61] The study was purely observational. After six months of treatment, patients were able to exercise longer, fewer had ST segment depression during treadmill testing, and there was a decrease in the incidence of effort anginal symptoms from 76% at baseline to 38% at follow up. The drug had no effects on heart rates or blood pressure which is consistent with its mode of action in reducing myocardial metabolic demands.

Albertsson et al treated 15 postmenopausal women with syndrome X using transdermal estradiol 17 beta.[62] The results were compared to placebo in a randomized control and also against 8 healthy volunteers. There was no effect on exercise time in controls but a significant increase in syndrome X patients. In syndrome X patients in addition, the times to angina and 1 mm ST segment depression were increased on active treatment but not placebo.

In 25 female syndrome X patients using 17 beta estradiol over an 8-week period, Rosano et al reported a reduction of symptoms compared to placebo which just attained statistical significance.[63] Unlike the study of Albertsson et al, there was no objective change in performance during exercise testing.

A move away from considering the problem merely in terms of a cardiac diagnosis may be called for. It is suggested that the terminology 'syndrome X' should be abandoned as this implies a certain cardiac diagnosis with a unified hypothesis and pathophysiology. Nothing could be farther from the reality. The patients seen in cardiology practice are likely to be similar to those who present to other specialities, such as gastroenterology or rheumatology clinics, who have unexplained physical symptoms. Symptoms without a conventional medical explanation may result from a complex interaction of biological, psychological, social and cultural factors. Certain physiological processes, including autonomic arousal, muscle tension, hyperventilation, vascular changes and the effects of inactivity, heighten bodily sensations, which may be felt as symptoms. Psychological hypotheses for the etiology of medically unexplained symptoms include the suggestion that the symptoms result from the patient's misattribution of normal bodily functions and sensations to a serious physical disorder. In some patients, medically unexplained symptoms are associated with psychiatric disorders, including anxiety, depression and phobia.[14] A failure to recognize these factors will inevitably lead to failure in management.

A common mistake in cardiology practice is to reassure the patient that their angiogram is normal but to continue management including medication as though they still have angina. A strong message that this is not a heart problem is likely to be more helpful and, to avoid conflicting signals, part of this message must include a decision to withdraw antianginal

drugs. It is important to acknowledge the reality of the patient's symptoms and to avoid trivializing. Other physical causes such as esophageal disorders or musculoskeletal pain should be considered.[64,65] Esophageal spasm and gastroesophageal reflux are commonly found but often show a poor temporal correlation with symptoms and treatment therefore seldom has effect on symptoms.[66,67]

Treatment with antidepressants may be useful, even where there is no evidence of depression. Before starting an antidepressant, it is important to explain to the patient that the drug is not being used to treat depression but to help symptoms. Benefit is usually seen within 1–7 days, which is before any antidepressant effect would be expected to occur. Sixty consecutive patients with normal coronary angiograms were entered by Cannon et al into a randomized controlled trial of imipramine vs placebo.[68] Twenty three (38%) had abnormal stress ECGs or gated radionuclide blood pool scans and, in 52 (87%) patients, their usual pain was reproduced by right ventricular pacing or infusion of adenosine into the coronary artery. After 3 weeks of active treatment, there was a 50% reduction in the number and intensity of symptoms. An improvement in mental state was observed but was also seen amongst patients receiving placebo. On repeat testing of right ventricular sensitivity there was a significant improvement while on imipramine but not placebo, which raises the possibility that the beneficial response may have been due to the effect of the drug on peripheral nerve receptors or the central processing of pain.

Conclusion

Chest pain and normal coronary angiography is a common problem. The absence of angiographic stenoses is associated with a good long term prognosis in terms of freedom from death and myocardial infarction, but many patients continue to report symptoms and remain functionally impaired. The cause of chest pain in most cases is uncertain. Abnormalities of coronary blood flow are commonly reported and support the view that arterial disease is present. These abnormalities however show considerable overlap between patient groups and are present in the normal population. There is no convincing evidence that myocardial ischemia occurs in the absence of angiographic stenosis, even where blood flow abnormalities are demonstrated.

The term 'syndrome X' should perhaps be abandoned since it implies a specific cardiac diagnosis. The term 'medically unexplained symptoms' is favored, as these patients share many features in common with patients presenting to other specialist clinics with unexplained symptom complexes. An approach to management that recognizes the importance of psychiatric, social and other non-cardiac factors is needed.

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Genetics in Cardiovascular Disease

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Introduction

The genetics of cardiovascular diseases is at an exciting stage of development, and it is appropriate to review where we are at present, and what may occur within the foreseeable future. In this relatively brief review, evidence that cardiovascular diseases do have a substantial genetic basis will be considered, the ways in which the individual genes can be identified will be reviewed and the implications of this information for future clinical practice will be assessed. As the results of human genome mapping project emerge, there will be an enormous wealth of information available on new biologic mechanisms which may influence the development, progression and outcome of cardiovascular disease. The concept of the 'post-genome challenge' for cardiovascular researchers has focussed research endeavors for some time.

The significance of genetic factors

The common cardiovascular disorders have long been recognized to arise through the interaction of environmental risk factors, such as lifestyle and individual susceptibility. This individual susceptibility may, in turn, be due to a combination of familial factors that are not themselves genetic with more overt genetically determined influences. For example, there is a substantial body of evidence that in utero environment determines programming of a large number of physiologic systems which are involved in the subsequent risk of adult cardiovascular disease.[1,2] Evidence in support of this has come from Barker's group and others in the form of longterm follow-up data, which are related to early life events.[3,4] In brief, there is an overall inverse relationship between size at birth and later risk of high blood pressure and other forms of cardiovascular disease. This relationship extends to risk of glucose intolerance, dyslipidemia and subtle changes in the function of the hypothalmic-pituitary adrenal axis.[5] Nonetheless, the precise relationship between fetal programming and subsequent cardiovascular risk remains to be defined. There are some data which suggest that part of the relationship may be determined by maternal cardiovascular function. For example, Walker has recently reported that small babies, who will have later risk of cardiovascular disease, also have a strong maternal history of hypertension.[6] It could be argued, therefore, that genes which predispose to maternal hypertension also regulate the fetal environment to result in reduced size at birth. Whether this directly

dictates adult cardiovascular risk or merely reflects a common genetic antecedent is unclear.

Despite these reservations, it is evident that there is a clear genetic component to cardiovascular disease. This is clearly seen in large-scale studies in human populations, particularly those that have used a twin paradigm to dissect out environmental and genetic factors. The majority of twin studies in a range of countries have indicated that monozygotic twins (genetically identical) share much closer resemblance of cardiovascular risk including hypertension, than do dizygotic twins who share only 50% of their genome.[7] There is equally strong evidence from the Montreal adoption study.[8] In this experiment, blood pressure similarities were compared in natural and adopted offspring and between natural and adopted siblings. In general, the correlation of blood pressure measurement was higher between mothers of natural children and fathers of natural children than between parents and adopted offspring. This relationship, which was seen for both mothers and fathers, tends to support the idea that maternal uterine environment cannot be the only explanation for subsequent adult cardiovascular risk. In addition, natural siblings showed a highly correlated level of blood pressure in comparison to adopted siblings. Thus, there is clear evidence that hypertension (and other cardiovascular disorders) do have a genetic component. Estimates suggest that this may contribute up to 30% of the variance in blood pressure within the population. The remainder of this review will concentrate on high blood pressure as a prime example of cardiovascular disease, in which substantial information about genetic factors is now available.

Single gene disorders

The search for the genes involved in hypertension and other forms of cardiovascular disease has accelerated over the last few years. In hypertension, a variety of approaches has been used. In many instances, the initial reference has been the study of single gene disorders where the genetic defect is well established and the link between genotype and phenotype is clear. There are, indeed, several single gene disorders which give rise to hypertension which have been thoroughly studied over the last few years.

Glucocorticoid remediable aldosteronism

Glucocorticoid remediable aldosteronism (GRA) arises as a consequence of an unequal crossover event during meoisis between the genes encoding corticosteroid 11 beta-hydroxylase and aldosterone synthase. This results in a fusion gene which possesses the 5' promoter region of 11 beta-hydroxylase (which includes ACTH responsive elements), and the 3' coding regions of aldosterone synthase, which results in a protein fully capable of aldosterone synthesis.[9] This gene, which is expressed throughout the adrenal cortex, results in primary aldosterone excess and consequent hypertension. The disorder is responsive to suppression with non-sodium retaining glucocorticoids such as dexamethasone.

Liddle's syndrome

Liddle's syndrome is an autosomal dominant disorder which is characterized by features of mineralocorticoid excess with suppression of plasma resin activity but, paradoxically, low

aldosterone levels.[10] The disorder is now known to be due to activating mutations affecting either the beta or gamma subunits of the epithelial sodium channel expressed in the renal tubule.[11] This protein is normally regulated by aldosterone action. In the mutated form, the cytoplasmic tail of the beta or gamma subunits is truncated, and this results in failure of interaction by the protein with other intracellular proteins so that cycling of the subunit and normal termination of its activity is faulty.[12] Blockade of the channel with the drug amiloride provides effective treatment.

Syndrome of apparent mineralocorticoid excess

The syndrome of apparent mineralocorticoid excess (SAME) occurs as an autosomal recessive condition and is, again, characterized by features of mineralocorticoid excess with suppression of plasma renin activity.[13] The abnormal sodium retention is due to the action of cortisol binding to mineralocorticoid receptors in the distal renal tubule. Normally, cortisol access to these receptors is prevented by the action of the enzyme 11 beta-hydroxysteroid dehydrogenase which converts cortisol to cortisone, which does not bind to the receptor. Where the enzyme is defective due to major mutations in both alleles, cortisol metabolism is severely diminished and the steroid is able to access the mineralocorticoid receptors and therefore mimic the effects of aldosterone.[14] The syndrome can be reproduced by drugs that inhibit the enzyme activity, such as carbenoxolone, and the syndrome responds to inhibition of cortisol production by non-sodium-retaining glucocorticoids such as dexamethasone.

Summary

There are a number of other rare autosomal dominant autosomal recessive syndromes, such as bradydactyly[15] and corticosteroid II beta-hydroxylase and 17 alpha-hydroxylase deficiencies[16] respectively. However, the majority of these rare well-characterized genetic disorders involve abnormal corticosteroid synthesis, metabolism, or renal tubular sodium retention as a result of this, or other rare mutations. These rare syndromes draw attention, therefore, to possible candidate mechanisms which may be altered in more common forms of cardiovascular disease by genetic factors. Indeed, a number of large-scale studies have examined the potential role of the genes involved in these rare syndromes in essential hypertension, and these are reviewed below.

There is considerable heterogeneity in the relationship between genotype and phenotype in these rare conditions. For example, within single kindreds with GRA, where the same genetic mutation is present, there is marked variability in the age of onset and degree of severity of hypertension.[17] This illustrates the concept that genetic factors, even when clearly identified, interact with other genes (epistasis) and with environment, to give rise to the ultimate phenotype.

Clinical studies

The above examples of rare genetic syndromes provide us with candidate loci that may be involved in commoner forms of hypertension. However, different strategies are necessary to identify whether these genes contribute to cardiovascular dysfunction. Candidate genes studies suffer from limitations in that they

only examine proteins whose function has been identified as potentially involved in cardiovascular regulation. Given that there are approximately 100 000 genes encoded within the human genome, it is likely that there are a large number of potential candidates which may be involved in cardiovascular regulation whose identity remains unknown. For this reason, alternative strategies that avoid a priori hypothesis are important for a thorough understanding of the genetic regulation of cardiovascular disease. The use of this alternative approach, which uses anonymous markers spaced evenly throughout the human genome, is discussed below.

Population case control studies

The simplest form of study of genetic factors in hypertension utilizes a population case control approach (Table 17.1). In this type of study, patients with hypertension are marched, as carefully as possible, with controls drawn from the same base population. The frequency of allelic variants of candidate genes within cases and controls is then compared, and when there is a significant difference between cases and controls, the role of the candidate is inferred. This approach has significant weaknesses. Firstly, it depends on the identification of suitable candidate genes in the first instance. Secondly, and more significantly, to match cases and controls, even in relatively homogeneous populations, can be extremely difficult. A number of studies of this type have been seriously flawed because of this difficulty.[18–20] Nonetheless, case control studies do have substantial power to identify genetic contributors to hypertension. Because of the large number of recombination events which must occur in a large cross sectional study within a population, any positive finding of a locus provides good evidence that the segment of DNA being studied contains a responsible gene.

Genetic study	*Advantages*	*Disadvantages*
Case-control	Simple to perform Substantial power	Need to identify suitable candidate genes Difficult to match cases and controls
Family-based linkage	Powerful in single gene disorders Examine multiple genetic markers	Less powerful in polygenic disorders Need numerous affected sibling pairs Loci identified may be distant from true QTL
Family association	Powerful study even with small numbers Study candidate genes and genome wide strategies	Need informative family structures

Table 17.1
Strategies for identifying the genetic basis of hypertension.

Family-based linkage studies

In single gene disorders, family linkage studies are a very powerful means of identifying responsible loci. For complex genetic disorders, such as hypertension, such studies are much less useful. However, modified forms of these types of studies, where the inheritance pattern of alleles is examined within sibling pairs, have more recently been used extensively. Thus, where a large number of affected sibling pairs with hypertension (or any other complex disorder) can be assembled, the inheritance by descent of a particular allele can be examined. Simple genetic principles dictate that siblings share, on average, no more than 50% of a single allele by descent, where the proportion of sharing is significantly increased from this, then the allele is implicated in the inheritance of the phenotype.[21] Such studies can utilize either candidate genes, or, importantly, a large number of loci, identified with a genome-wide search to examine multiple genetic markers.

At present, data from full genome searches of this type in hypertension are still preliminary. However, limited investigations using this type of approach have revealed quite interesting results. First, several groups have used the population ascertainment described here to explore candidate regions thought to be involved in blood pressure regulation or in hypertension. One such study found evidence of a locus on chromosome 5 that includes genes encoding the beta-2, alpha-1b and dopamine-1 receptors that was linked to blood pressure regulation in a population of discordant sibling pairs.[22] A more recent report identified the same locus in a hypertensive population using a family-based approach.[23] Other groups have reported positive findings with the region on chromosome 17 that is syntenic with a quantitative region from rat chromosome 10. For example, positive linkage has been detected for the longterm systolic blood pressure trend in the Framingham population following a genome-wide scan.[24]

However, the affected sibling pair approach, although relatively simple in design, is not particularly powerful.[25] Loci that are identified may be genetically quite distant from the true quantitative trail locus, as within the two-generation model, only a relatively small number of recombination events will occur. In addition, studies of this type lack statistical power: large number of siblings are necessary to identify loci that have, in themselves, relatively weak relative risk.

Family association studies

A more powerful approach that avoids a number of the problems identified above is to utilize family structures within a family association model. In this type of study, the transmission of candidate alleles is examined from parents to index cases with the disorder.[25] The frequency of alleles in the index cases can be predicted from the frequency in the parental generation; where this is significantly distorted (transmission disequilibrium), the allele in question is implicated in the disorder. This type of approach uses, in effect, the parental allele frequency as an internal control for the affected cases. The power of this type of study is relatively high, and mathematical predictions suggest that relatively small populations can be used to generate useful data.

However, at present few studies have attempted to utilize this design in practice. In theory, this type of study can be used both with known candidate genes and with a

genome-wide strategy with anonymous markers. Again, no data are currently available to show that this approach does work, although mathematical modelling predicts that it will be of use in identifying relevant genes that contribute to hypertension and other cardiovascular disorders.

Candidate gene studies

Notwithstanding concerns over candidate gene studies in hypertension, such investigations have identified potential loci and mechanisms of the genetic basis of the condition. Many of these positive findings have focussed attention on genes that encode components of the renin angiotensin/aldosterone system (Fig. 17.1) or on renal sodium handling.

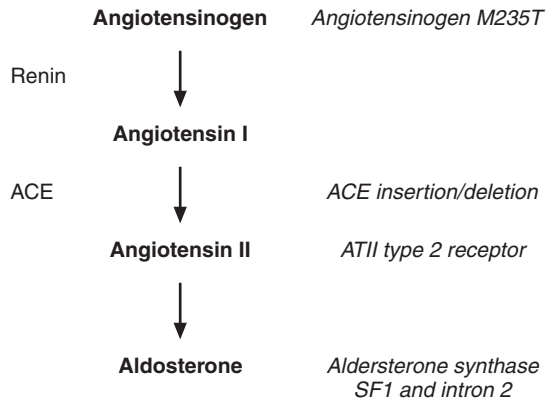

Figure 17.1
Polymorphisms identified within the renin-angiotensin system.

Angiotensinogen

The angiotensinogen gene encodes the protein which is cleaved by renin to yield angiotensin I. Initial studies suggested that angiotensinogen levels were higher in families with a strong history of high blood pressure, which drew attention to the locus.[26] Since then, a number of polymorphisms associated with the angiotensinogen gene have been identified. Two intragenic variations are in close linkage disequilibrium: one (M235T) is associated with variation in plasma levels of angiotensinogen.[27] In case/control studies, this variant is also associated with hypertension and with an increased requirement for antihypertensive therapy.[28] A recent meta-analysis examined eleven association type studies of this variation in a large number of predominantly white populations.[29] These studies, which included a total of approximately 5000 patients, showed variable effects of this polymorphism on blood pressure, although the pooled data did suggest that an association between the angiotensinogen marker and hypertension overall. However, it is appropriate to note that meta-analyses have significant weaknesses. An alternative marker is a polymorphic region in the 3' untranslated region of this gene, which is highly informative for linkage type analysis. A joint investigation using this marker in affected sibling studies in both the United States and Paris reported a positive finding between this marker and hypertension,[27] and similar data were reported from an Afro-Caribbean population in Jamaica.[30] Despite these initial optimistic reports, a more recent finding from the European Consortium on genetics of hypertension failed to show any association between this marker and hypertension.[31] Thus, at present,

the status of the angiotensinogen locus remains uncertain.

Angiotensin converting enzyme

The potential of the angiotensin converting enzyme (ACE) gene as a locus for hypertension was initially identified in studies of rodent hypertension where association between chromosome 10 and high blood pressure was found in classical breeding studies.[32] The ACE gene was close to the quantitative trait locus (QTL) identified in this cross, although subsequent investigations have not confirmed the role of ACE in rat hypertension. Nonetheless, there is a by-allelic polymorphism within the ACE gene (intron 16) which associates with variations in plasma levels of ACE protein and ACE activity, and this provides an attractive candidate for hypertension.[33] Ueda et al have shown that this polymorphism is associated with altered generation of angiotensin II in vivo,[34] and that this determines, in part, the responsiveness to single doses of the ACE inhibitor, enalaprilat.[35] Initial studies, using case/control and family-linkage analyses, have not shown any association with hypertension.[36,37]

More recently, however, analysis of the large Framingham population in the US have suggested that the D allele of the ACE gene (which is associated with higher ACE levels) is associated with hypertension in male subjects only.[38] Another US study has also identified an association with high blood pressure.[39] Interestingly, there has been evidence from meta-analysis that the ACE locus is also associated with increased risk of vascular disease, including myocardial infarction, peripheral vascular disease and stroke (Table 17.2).[40] However, more recent evidence from the ISIS study has not been able to demonstrate any major influence of this locus on risk of myocardial infarction.[23] Thus, the evidence that ACE is important in cardiovascular risk is very limited, and there remains doubt about its role in the development of hypertension.

Disease state	*Number of subjects*	*Odds ratio DD vs II*	*Confidence interval*
Hypertension	6923	1.10	0.95–1.27
Left ventricular hypertrophy	3285	1.05	0.81–1.36
Coronary heart disease	18 325	1.32	1.21–1.45*
Myocardial infarction	11 050	1.45	1.29–1.62*
Stroke	1674	1.94	1.45–2.60*
Peripheral vascular disease	926	2.33	1.51–3.58*

Abbreviations: DD – Homozygotes for the deletion allele, II – Homozygotes for the insertion allele, C.I. – Confidence interval, * * $p < 0.001$.

Table 17.2
Adapted from Staessen et al meta-analysis.[40] Association between disease and deletion allele of the ACE polymorphism.

Angiotensin II receptor

The angiotensin II receptor (Type I) regulates the vasoconstrictive effects of the peptide, and is involved in effects of angiotensin II on endothelial function and in regulation of vascular smooth muscle cell growth. Thus, variations in the function of this receptor would be attractive as a candidate mechanism, which might subserve the genetic basis of hypertension. There is relatively little information on the angiotensin II receptor in this regard. A single nucleotide polymorphism within the gene has been identified which appears to be associated with altered vascular compliance,[41] but there is no evidence that the polymorphism is associated with high blood pressure. Indeed, studies of this association have been negative.[42,43]

Aldosterone synthase

Aldosterone synthase is the enzyme that regulates the terminal conversion of deoxycorticosterone to aldosterone in the adrenal cortex. The gene, which is expressed in the zona glomerulosa of the adrenal, is implicated in the genetic pathophysiology of the rare, monogenic form of hypertension, GRA (see earlier). Polymorphisms associated with aldosterone synthase include a single nucleotide variation in the 5' promoter region at position −344.[44] This polymorphism alters the binding of a steroidogenic factor that might, potentially, change expression of the gene within the zona glomerulosa. This polymorphism is in tight linkage disequilibrium with another variation which results in conversion of intron 2 of the aldosterone synthase gene to the intron of the immediately adjacent gene encoding corticosteroid 11 beta-hydroxylase (Fig. 17.2).[44]

Two studies have reported positive associations between the T allele of the 5' promoter polymorphism and hypertension (both of these are case-control studies). One study also examined this polymorphism in a limited affected sibling study and could find no positive association with high blood pressure.[45] In the positive case-control study with the T allele, increased levels of aldosterone in subjects with this variation were also noted.[46] In a separate population, an association between the other allele of this gene and left ventricular hypertrophy has been reported.[47] The significance of this finding remains uncertain and, as the result was marginal, more detailed investigation of this polymorphism with left ventricular function and structure is necessary.

Adducin

Adducin is a membrane-associated protein that regulates the activity of $Na^{-}K^{+}$-ATPase. The adducin gene was initially implicated in hypertension in the Milan strain of rat.[48] More recently, a mutation in the alpha-subunit of the adducin gene has been reported to be associated with high blood pressure using both

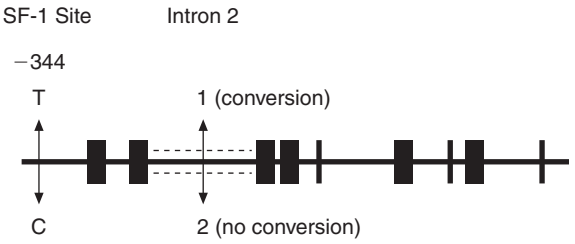

Figure 17.2
Polymorphisms within the CYP11B2 (aldosterone synthase) gene.

case-control and linkage approaches.[49] However, as with many other polymorphisms, investigations in other populations have not confirmed these initial positive findings.[50,51]

In the rat, the adducin gene variation is associated with salt-sensitive hypertension.[52] Studies in humans have, therefore, examined the relationship between the adducin mutation and sodium sensitivity. The mutation in the alpha-subunit, described above, is also said to be associated with significant sodium sensitivity and, interestingly, with an increased hypotensive response to thiazide diuretics.[49] Again, however, this study needs to be replicated in other populations before it can be fully accepted.

Epithelial sodium channel

The epithelial sodium channel, which is discussed above in relation to Liddle's syndrome is also a potential candidate gene in essential hypertension. At present, only one study has examined this in a population/case/control investigation. Baker and colleagues examined the frequency of a relatively rare polymorphism with the beta-subunit of the sodium channel and reported an increased frequency in black hypertensives.[53] This finding needs to be confirmed in other populations.

Summary

Candidate gene studies have all concentrated, as indicated, on components of sodium-retaining mechanisms or hormones associated with salt balance. Other studies have investigated polymorphisms associated with the genes involved in endothelial function (for example, eNOS), and have had similarly variable results.[54,55] At present, therefore, there remains uncertainty about many of the potential candidate genes and their role in both hypertension and other forms of cardiovascular dysfunction. Of the available data, the ACE gene polymorphism has been the most thoroughly studied: there are compelling data that the polymorphism is associated with altered physiologic function. Furthermore, there are studies that suggest the ACE gene may be associated with altered response to hypertensive therapy, and this type of information will be discussed further below.

Future directions

Information may help on the genetic basis of hypertension in a number of ways: to target subjects at particular risk of cardiovascular disease or its complications; to develop new drugs or make better use of existing agents; and to give a clearer understanding of the underlying pathophysiology of cardiovascular disease, which will enable practitioners to modify lifestyle and other environmental factors more effectively.

In the absence of convincing and consistent data from candidate gene studies, it is reasonable to ask if current information allows the modification of existing therapeutic strategies. As mentioned above, data on the ACE gene polymorphisms suggest that subjects with the D allele of the ACE gene generate more angiotensin II in vivo, and may be relatively resistant to a single dose of an ACE inhibitor.[31] A further study also indicated that subjects bearing the D allele of the ACE gene polymorphism were relatively resistant to ACE inhibitor therapy over longer-term dosage.[56] Thus, subjects with the D allele showed a smaller fall in blood pressure and a lesser reduction in urinary albumin excretion than

those with the I allele. Again, this reported finding needs to be confirmed in other, larger and more powerful studies. If confirmed, however, it suggests that the ACE gene polymorphism offers a simple test which would identify those subjects who might require more aggression anti-hypertensive therapy or more intensive treatment with an ACE inhibitor.

The current status of studies into the genetics of cardiovascular disease remains unsatisfactory. At present, there are a large number of contradictory reports on a relatively limited number of candidate genes. The most appropriate way to identify important loci would be to perform large-scale, suitably powered, studies which can provide comprehensive coverage of the human genome using a genome-wide search. This type of approach is now being carried out in studies in both the US and the UK. In the UK, the MRC funded BRIGHT study is one such example. Until data from these investigations are available, it is hazardous to speculate about the relative importance of existing candidates. The information from these large-scale studies and the dividend from the human genome-mapping project may well identify new and hitherto unsuspected loci, which may be important in cardiovascular disease. These may lead, in turn, to new methods of drug development and targeting of patients at high risk.

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18

Cardiac Rehabilitation

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Introduction

The psychological and physical rehabilitative needs of the patient with cardiovascular disease will be outlined in this chapter, followed by presentation of current recommendations for content and delivery of cardiac rehabilitation. The evidence base for the effectiveness of cardiac rehabilitation interventions will be outlined along with key issues such as current provision and participation rates amongst different patient groups. With the demand for cardiac rehabilitation growing to include not only patients who have suffered myocardial infarction (MI), but also previously excluded groups such as patients with heart failure or chronic stable angina, the evolving arena for the future of cardiac rehabilitation will be considered.

Cardiac rehabilitation has been defined by the World Health Organisation as:

> '. . . the sum of activities required to influence favourably the underlying cause of the disease, as well as the best possible, physical, mental and social conditions, so that they [people] may, by their own efforts preserve, or resume when lost, as normal a place as possible in the community. Rehabilitation cannot be regarded as an isolated form or stage of therapy but must be integrated within secondary prevention services of which it forms only one facet.'[1]

Historical perspective

In the 18th century, Heberden noted one of the earliest cases of a patient with coronary heart disease who benefited from exercise, by sawing wood for half an hour a day for 6 months, and was 'nearly cured' of his angina.[2] This observation was not heeded by physicians in the 19th century, who prescribed complete bedrest for post-myocardial infarction patients for 6 weeks after the event. However, in the 1950s and 1960s, two centuries after Heberden made his observation, the first coronary rehabilitation programs in Israel and Ohio consisted largely of exercise training for periods of up to 5 years following MI.[3]

It is now recognized that exercise training alone is insufficient. The American Heart Association (AHA) has published a position statement stating that interventions comprising exercise training only were not considered cardiac rehabilitation.[4] Thus, as defined by WHO (see above), cardiac rehabilitation is a process that should not only enable physical and psychological recovery to promote

participation in usual (or appropriately modified) occupational and social activities, but should also enable the patient to recognize and influence risk factors to prevent further development of atherosclerosis. Cardiac rehabilitation thus entails a multi-disciplinary approach which comprises psychological support, exercise and education, with support from doctors, nurses, physiotherapists, occupational therapists, pharmacists, dieticians and clinical psychologists/liaison psychiatrists.

Commonly, the term cardiac rehabilitation has been synonymous with a structured inpatient, or most usually outpatient, course that involves exercise and incorporates education, relaxation and other essential components. However, cardiac rehabilitation should start during hospitalization and continue for life. The structured intervention program that is offered to patients occurs during what is defined in the UK as phase three of the cardiac rehabilitation process (see later).

In recent decades, the development of cardiac rehabilitation services has been uncoordinated, with variation in provision both within and between countries. In early UK programs, specialist nursing staff took the lead in providing cardiac rehabilitation, usually with support from physiotherapists and occupational therapists, but, unfortunately, less frequently from doctors. Organizing bodies have now been developed in many countries in order to provide evidence-based guidelines and to encourage provision of services. The American Association of Cardiovascular and Pulmonary Rehabilitation (AACPR) have recently published detailed and comprehensive guidelines regarding cardiac rehabilitation/secondary prevention programs.[5] European guidelines are summarized in the Carinex Survey.[6] The AHA has further developed their position statement for cardiac rehabilitation and recently, along with the American Association of Cardiovascular and Pulmonary Rehabilitation (AACPR), has produced a scientific statement that details core components and expected outcomes for cardiac rehabilitation/secondary prevention programs[7] (see later). Most recently, in the UK, the importance of cardiac rehabilitation is recognized by its inclusion in the National Service Framework for Coronary Heart Disease:[8]

> 'NHS Trusts should put in place agreed protocols/systems of care so that, prior to leaving hospital, people admitted to hospital suffering from coronary heart disease have been invited to participate in a multidisciplinary programme of secondary prevention and cardiac rehabilitation. The aim of the programme will be to reduce their risk of subsequent cardiac problems and to promote their return to a full and normal life.'

Funding for cardiac rehabilitation programs in the UK was provided in the late 1980s through the British Heart Foundation (BHF) and Chest, Heart and Stroke Association (CHSA). Many programs have developed since this time, although there is still not unity in provision or adherence to recommended guidelines. The support of the BHF ensures some continued funding but, although funding is also sometimes provided locally, financial constraints still lead to shortfalls in provision of service.

Exercise

Many patients and staff associate cardiac rehabilitation with exercise training, although

it represents just one component. Cardiac patients may feel limited in terms of their physical and exercise capabilities and may need encouragement and support from staff in order to gain confidence to return to or increase their previous activity levels. Staff should feel confident in prescribing and encouraging individual exercise regimes. A comprehensive review of exercise training as a component of cardiac rehabilitation is beyond the scope of this chapter, however the following section highlights key points regarding the suitability of exercise training for specific patient groups (Table 18.1).[9,10]

	Target heart rate (THR) as determined by exercise treadmill test (ETT)	*Risks*	*Comments*
Myocardial ischemia (not at low workloads)	Maximal THR: 10 bpm below that at which ischemic abnormalities occur	Increase monitoring e.g. ECG monitoring during initial stages	Should first receive maximal therapy to alleviate ischemia
Heart failure	Maximal THR: 10 bpm below that at which significant dyspnea and fatigue occur	May be at higher risk for exercise-based complications but may make most significant improvements	Less likely to benefit from exercise if inducible ischemia is present
Ventricular arrhythmia	If severe on ETT, patient usually excluded from exercise training until arrhythmia suppressed	A stable pattern of arrthymia during ECG-monitored exercise sometimes precedes supervised but unmonitored exercise. However, the safety of this has not been formally assessed	If coronary disease and exercise-induced ventricular arrhythmias are present, there is high risk of fatal events and non-fatal ischemic complications.
*Pacemaker	Value of ETT may be limited: may be used to determine optimal programming for pacemaker, can determine exercise capacity and ensure correct function of pacemaker		Heart rate response is dependent on type of rate adaptive sensor. Type of pacemaker will also determine exercise recommendation

Table adapted from Dennis 1997.[9]
*Adapted from Sharpe et al, 1998.[10]

Table 18.1
Exercise recommendations in cardiac rehabilitation.

Exercise training has been shown to be beneficial in patients recovering from MI, coronary artery bypass graft surgery (CABG), coronary angioplasty, valve surgery and cardiac transplantation, as well as in patients with stable angina and compensated congestive heart failure.[9,11,12] A reduction in exercise-induced ischemia (determined by ST segment depression[13–15] or thallium perfusion abnormalities[16,17] has been demonstrated as a result of extended high intensity exercise training, although the exact mechanism remains undetermined. Patients with coronary heart disease who have undergone exercise training have also demonstrated improvement in submaximal endurance capacity, demonstrating an increase in total exercise time with a lower heart rate and blood pressure response than that attained pre-training.[12,18] In the elderly population, an increase in exercise capacity is also achieved through exercise training but does not persist after cessation, which highlights the need for continued training.[19]

Although many studies involve mainly young male patients, women and the elderly also benefit from exercise training and should not be excluded.[19–24] Usually, an exercise treadmill test will establish the safety and direct the capacity for exercise training. A modified Bruce protocol can be used for exercise treadmill testing 7–21 days following uncomplicated MI, 3–10 days following angioplasty and 14–28 following surgery. If a patient is unable to cope with a treadmill test because of anxiety about the treadmill, they may be assessed with the use of an exercise bike. In those patients who are unable to undertake exercise treadmill testing because of comorbid reasons such as arthritis, the exercise prescription should be individually tailored.

Sexual activity

Sexual problems are common and very often unrecognized amongst the cardiac population and their partners. Patients and their partners may have concerns regarding resumption of sexual activity after cardiac events as well as after therapeutic interventions. Many patients mistakenly believe that resuming sexual activity may compromise the health of their heart, placing undue strain on the heart with risk of further chest pain or re-infarction. Patients should be assessed as to their suitability for return to physical activity according to the stability of their cardiac condition. When stable, they and their partners should be reassured that sexual activity places no greater strain on the heart than other daily activities, such as housework or gardening (Table 19.2). It is important that discussion regarding the fears and concerns of resumption of sexual activity should take place with the partner, as they are likely to be as anxious, or more so, than the patient.

With regard to risk associated with sexual activity, the baseline absolute risk of having a MI, for a healthy adult, is approximately one per million per hour. The risk of a patient with a history of MI suffering a further MI during, or in the two hours after sex, rises to about three times above this baseline level. In an individual without cardiovascular disease the increase in risk is about 2.5 fold above baseline. Thus, there is minimal cardiac risk associated with sexual activity in the general population and this is not significantly increased in patients with stable cardiovascular disease.[25,26]

As well as having concerns about resumption of sexual activity following a cardiac event, between 39% and 64% of male cardio-

Activity	*METs score rating (metabolic equivalent of the task)**
Sexual activity with a longterm partner:	
'normal' activity	2–3
'vigorous' activity	5–6
Housework:	
Heavy, e.g. making beds, scrubbing floors	3–6
Light, e.g. ironing, polishing	2–4
Lifting and carrying objects (9–20 kg)	4–5
Gardening (digging)	3–5
Golf	4–5

*1 MET = relative energy demand of oxygen used in the resting state, approximately 3.5 ml oxygen/kg body weight/minute. Adapted from Jackson et al, 1999.[25]

Table 18.2
Level of exertion of typical daily activities.

vascular patients suffer from erectile dysfunction (ED),[27] much higher than the estimated prevalence for ED in the general population. Cardiac rehabilitation staff should be able to broach this subject sensitively with the patient and refer for appropriate assessment and treatment as necessary. Published guidelines for assessment and treatment are available and, in the majority of patients with ED and cardiovascular disease, this can take place in a primary care setting.[25] In patients who are defined as high cardiac risk, specialist confirmation should be given that the cardiovascular condition is stable prior to treatment in primary care. There is no evidence that currently licensed treatments for ED will add to overall cardiovascular risk.[25]

The concerns, and thus the rehabilitative needs, regarding sexual activity may differ between men and women according to cardiac diagnosis. In a small but in-depth interview study of patients following CABG, women were more likely than men to be concerned with the impact of scarring affecting their sexual desirability and intimacy. Men were more likely to view their change in body image as a display of courage or 'enhancement' of self esteem.[28] However, in a study of 462 men and 51 women, Drory et al report men and women to be affected similarly with regard to frequency of, and satisfaction with, sexual activity 3–6 months following first acute myocardial infarction (AMI).[29] The sociodemographic variables, age and education, showed a statistically significant relationship with sexual behavior before and after AMI. Also, in men and women, lower perceptions of health before MI were significantly related to less and lower quality of sexual activity before and after MI. Generally, studies

of sexual activity in patients following AMI, particularly those also including women, have included small patient numbers, producing conflicting results and thus restricting their value in extrapolation.[30]

In the patient who has suffered a cardiac event or who has a diagnosis of coronary heart disease, recognition should be given to possible impact on sexual functioning. Consideration needs to be given to what can be done to improve the knowledge and confidence of health care professionals in discussing a sensitive topic of this kind during cardiac rehabilitation.

Psychological aspects

Historically, much was made of the type A personality which the cardiologists Meyer Friedman and Ray Rosenman used to describe their patients.[31] Recently it is the hostility component of type A behavior that has received attention. It is the expressed aspects of hostility, such as verbal and physical aggression, rather than subjective feelings or thoughts, which have been shown to be associated with coronary heart disease,[32] although there is limited evidence regarding outcome of interventions to reduce hostility in patients with CHD.[33] Attention is currently focused on the anxiety and depression experienced by many patients with CHD, although the support needed will vary both according to cardiac diagnosis and individual psychological strengths and weaknesses of the patient.[34]

Most commonly patients may experience anxiety and/or depression and, in extreme cases, may demonstrate cardiac neurosis. Anger and denial may also be experienced. The psychological state of the patient, whether post-MI, with current stable angina, or post-coronary intervention, will influence the rehabilitative process. It may impact on the patient's willingness to participate in or to adhere to a structured cardiac rehabilitation program, or to follow secondary prevention advice such as taking medication.[35] Theoretical developments in the relatively new discipline of health psychology[36] have provided models or frameworks of health behavior which have now been studied in patients with coronary heart disease in an attempt to explain adherence to treatment advice. Leventhal et al[37,38] propose a model in which the views or beliefs that patients hold about their illness are key issues in directing their self-management.[37,38] The results of studies on the impact of illness beliefs on recovery from MI and CABG, including cardiac rehabilitation attendance, will be discussed below.

Anxiety and depression

Anxiety and depression following MI or diagnosis of a cardiac condition is a common and expected response to what is a life-threatening (in the case of MI) or 'loss' (of one's health status) event. Up to one third or half of patients who suffer MI will experience anxiety and depression. High levels of anxiety are to be expected on hospital admission and at the time of discharge, but these should subside and cease after a period of time at home. Many patients and their families are warned that the patient will experience a 'homecoming' depressive mood state but, again, this should subside over time. Unfortunately up to 15–20% of patients show the presence of severe depression following MI, and major depression during hospitalization has been demonstrated to be an independent risk factor for increased mortality within the first 6

months.[39] Moreover, an 18 month follow-up study of MI patients demonstrated an independent relationship between mild to moderate depression and 18-month cardiac mortality.[40] The diagnosis and management of depression in the patient with CHD is realistically described as 'a clinical and interdisciplinary challenge' in an excellent practical review of the topic.[34]

The presentation of symptoms in cardiac patients may be less typical than those in psychiatric patients. Typical feelings of sadness, low self-esteem, guilt and death may be replaced by anxiety (chronic worries, hypervigilance, multiple somatic complaints) and irritability (outbursts of anger and hostility, negative and unpleasant comments to others.) As well as attributing somatic symptoms, such as atypical chest pain, dyspnoea and palpitations, to their heart disease, patients will also be likely to complain of excessive tiredness or lack of energy.[34]

Although participation in a cardiac rehabilitation program should enable the identification of patients who may be clinically depressed, participation will not be sufficient to identify and address the specific treatment needs of the patient. Referral to either a clinical psychologist or liaison psychiatrist in order to treat and reduce the depression will be necessary before the patient is able to undertake lifestyle behavioral changes to modify risk factors for CHD.

Patients who suffer from chronic stable angina, and who do not fully understand the nature of their heart condition, may reduce their physical activity through anxiety and fear of provoking further attacks. This will lead to a decrease in their exercise capacity and ability to carry out activities of daily living, and thus reduce quality of life. It is important that such misconceptions are addressed as part of cardiac rehabilitation to prevent this detrimental cycle.

Hospital Anxiety and Depression Scale

In the first instance, identification of patients who warrant further intervention should be relatively straightforward through the use of a screening tool such as the Hospital Anxiety and Depression Scale (HADS).[41] This is a fourteen-item state measure, with seven items each for anxiety and depression. The measure was developed for use in medical outpatient clinics and the scores are not influenced by physical symptomatology. Importantly, the questionnaire is acceptable to patients, takes only a few minutes to complete and may be repeated over time to assess change. The questionnaire is simple to score: from 8 to 10 on each scale indicates a possible clinical disorder and, from 11 to 21, a probable clinical disorder. (These scores resulted in fewest false positives and false negatives when compared with psychiatrist assessment). Score ranges may also be classified as 'normal' (0–7), 'mild' (8–10), 'moderate' (11–14) and 'severe' (15–21).

As persistent distress can have a detrimental impact on the post-MI patient, it has been suggested that patients should be routinely asked to complete the HADS when attending for their outpatient exercise treadmill test at 6–12 weeks post-discharge from hospital.[42] This would enable screening of those patients who are not attending a structured cardiac rehabilitation course (perhaps those who are more likely to be depressed), and referral for appropriate management from a psychologist or liaison psychiatrist.

Patients' understanding

The 'commonsense' self-regulatory model suggests that patients' own key perceptions of their illness are critical in guiding their coping efforts to deal with symptoms, illness and threats to health.[38,39] According to this model, patients' illness beliefs have been shown to be organized around five central themes:

- the patient's understanding of causal attributions: the cause(s) of the illness
- timeline: whether the illness is cyclical, short-term, longterm
- control: whether the patient feels they can personally influence the course/outcome of the illness
- identity: the symptoms/signs that the patient associates with the illness
- consequences: the impact of the illness on the patient's life, i.e. employment, relationships

Illness beliefs can be assessed using a validated tool, the Illness Perception Questionnaire (IPQ)[43] and two studies have used the IPQ to examine the role of patient illness beliefs following MI. The New Zealand Heart Attack Study followed 143 male patients post MI for six months.[44] The baseline measures (taken during hospitalization) of illness perceptions were correlated with 6 month follow-up outcome measures, including time to return to work, physical and social functioning, sexual functioning and attendance at a cardiac rehabilitation course. Attendance at the rehabilitation course was significantly related to the patient holding a stronger belief that they had some degree of personal control over the future course of their illness. Return to work within 6 weeks was predicted by the perception that the illness would last a short time and have less grave consequences for the patient. Belief that heart disease would have serious consequences was significantly related to later disability in work around the house, recreational activities and social interaction. A strong illness identity (association of many symptoms with the illness) was significantly related to greater sexual dysfunction at both 3 and 6 months. The influence of key illness beliefs was independent of clinical measures of severity of MI. In the second study, carried out in two centers in the UK,[45] baseline measures of illness beliefs were obtained during hospitalization for MI or CABG in 152 patients. Patients were followed up at 6 months and the main outcome measure was attendance at cardiac rehabilitation. Those patients who, during initial hospitalization, had made a causal attribution to some aspect of their lifestyle for their heart condition, e.g. smoking, lack of exercise, poor diet, were more likely to have attended a cardiac rehabilitation course as were those who felt they had some degree of personal control over the course of their heart condition (rather than it being all down to 'fate' or 'chance').

It would appear that patients' initial illness beliefs are important determinants of recovery after MI or CABG, including return to work, cardiac rehabilitation attendance, physical, social and sexual functioning. Specific illness beliefs and misconceptions need to be routinely elicited from patients at an early stage, preferably during hospitalization for a cardiac event, in order that they can be targeted to optimize recovery.

Cognitive-based interventions

Cognitive therapy is based on the premise that an individual's thoughts and mood will shape

their behavior with a subsequent impact on their feelings of well-being and quality of life. Cognitive therapists use varying interventional methods according to the complaints that they are addressing. An essential first stage of an intervention is to enable the patient to recognize that misguided beliefs may have a negative influence on their behavior and subsequent well-being. A patient with angina may be worried that social- or work-related physical activity may increase their risk of chest pain or heart attack and thus avoid physical activity, which in turn has a negative impact on employment status, social functioning and relationships. The resulting physical deconditioning would further confirm their fears and concerns regarding their fragile state of health. Addressing 'faulty' thoughts should interrupt such negative cycles. Relaxation methods may also be taught to control physiological symptoms of anxiety. There is evidence for the effectiveness of cognitive behavioral approaches for addressing a range of common disorders, including anxiety and depression.[46]

Recent UK guidelines and audit standards state the need to address misconceptions held by patients with regard to their coronary heart disease in order to reduce distress and optimize outcome.[47] One home-based cardiac rehabilitation program in Scotland successfully does this in patients who have suffered MI with an intervention which comprises a self-help 'heart manual' relaxation tape and taped interview between a patient and doctor.[48]

A cognitive behavioral approach has been successfully applied in patients with angina. An anxiety management program was undertaken by 80 patients, 28 of whom were awaiting CABG.[49] The results at 1-year follow-up were impressive. A third of patients reported no angina, approximately three quarters reported a reduction in anginal episodes and in self-reported disability. Symptom reporting improved to such a degree that 50% of the patients who were awaiting CABG were removed from the waiting list following assessment by their cardiologist.

Further collaboration between those involved in the care of the CHD patient and cognitive therapists should prove fertile ground for improved interventions and patient outcome.

Partner involvement

It is important that cardiac rehabilitation interventions involve as much as is possible the partner and family of the patient. Both the patient and partner are likely to experience anxiety and, in some cases, the partner may experience greater anxiety and/or depression than the patient. In patients who have suffered MI, it may be helpful for the partner to watch them perform the exercise treadmill test. This will reassure the partner about the patient's capacity for resumption of physical activity and may prevent them from shielding or overprotecting which could have a negative impact on the patient's activity levels and might become a source of conflict. The overprotection by a partner may result in some degree of role reversal which can lead to anger or frustration for the patient.

Effectiveness of cardiac rehabilitation

Since 1990, much research has centered on establishing whether cardiac rehabilitation programs improve morbidity and mortality. A meta-analysis of 22 randomized trials of cardiac rehabilitation that involved exercise in 4554 patients who had suffered MI showed a

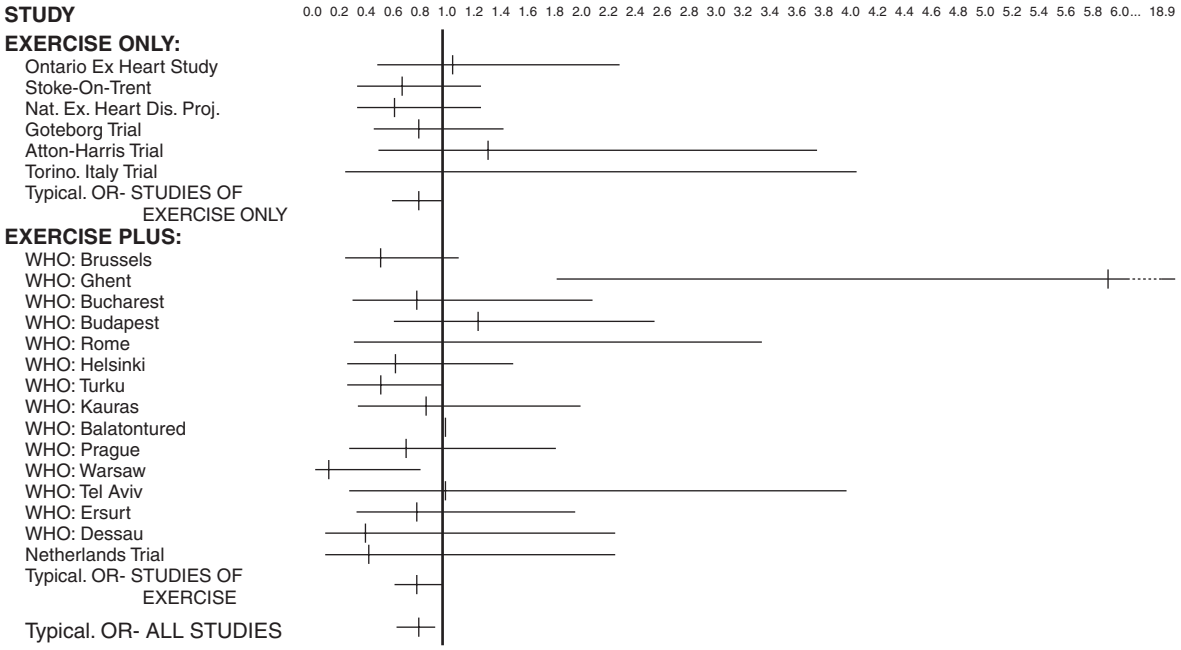

Figure 18.1
Estimate of mortality 3 years after randomization for trials of cardiac rehabilitation (odds ratios and 95% confidence intervals). Reproduced with permission from O'Connor et al, 1989.[50]

decrease in overall mortality of 20%.[50] This reflected a decrease in cardiovascular mortality and fatal reinfarction throughout the first 3 years (Fig. 18.1). A reduction in sudden death was shown for 1 year post-infarction and possibly for 2 and 3 years. There was no significant difference for nonfatal reinfarction. Similarly, a meta-analysis of 10 randomized controlled trials demonstrated a reduction of approximately 25% for cardiovascular and all-cause mortality in the intervention group compared to usual care in the control group.[51] It was not possible to compare the impact of 'exercise only' with a multifactorial approach in these analyses.

A meta-analysis that attempted to evaluate the additional impact of psychosocial intervention during rehabilitation on physical and psychological aspects of recovery reported a reduction in mortality, morbidity, psychological distress, blood pressure, heart rate and cholesterol level in the 2 years following MI.[52] However, the methodology has subsequently been criticized and the validity of this finding questioned.[53] Likewise the effectiveness of formal programs has been questioned following the publication of two studies. The results of a multi-center controlled study demonstrated no benefit to post-MI patients who were referred to a rehabilitation program that comprised psychological therapy but excluded usual components of a multidisciplinary program, such as exercise, smoking and dietary advice.[54] The Montreal Heart Attack Readjustment Trial, a home-based psychological intervention in patients who had suffered

myocardial infarction reported greater mortality in women in the intervention group compared to the control group.[55] However, in support of formal cardiac rehabilitation programs it has been argued that current cardiac rehabilitation guidelines have been developed from a substantive body of evidence that supports the role of cardiac rehabilitation in reducing anxiety and depression and cardiac mortality. The studies mentioned above deviated in content from such guidelines and methodological flaws have been raised regarding the second study.[56] Ideally all patients should be offered a menu-based option of intervention according to their need and those with persisting and clinically relevant psychological problems should receive individually tailored intervention.[57]

Establishing the evidence base for effectiveness of cardiac rehabilitation interventions is all-important but the difficulty in distinguishing which aspect of a multifactorial intervention has produced which change in psychological or physical outcome will continue to present a challenge.

Recommendations for delivery

Cardiac rehabilitation can be divided into four phases as shown in Table 18.3 (in many European countries phases II and III are combined). According to UK guidelines,[42] three associated elements should pervade these phases:

- Accurate and regular explanation of the medical diagnosis and management with facilitation of understanding
- Individually tailored specific intervention, the outcomes of which should be stated and assessed
- The process of re-adaptation and re-education, mapping to long-term rehabilitation.

Initial patient assessment is fundamental to success and should include:[5]

- Medical history
- Physical examination
- Testing
  - physiological: including ECG, ETT, lipids, diabetes
  - psychological: including quality of life (MOS SF-36), anxiety and depression (HADS), and sexual functioning questionnaires
- Written patient evaluation and care plan with detailed priorities (short and long term goals and strategies) for risk reduction and rehabilitation
- Ensure patient and primary healthcare provider are aware of the care plan

Follow-up should include:[5]

- assessment of quality of life changes (questionnaires)
- written summary of patient outcomes which details further specific intervention and monitoring

Core components of cardiac rehabilitation should include psychosocial management, physical activity and dietary counseling, exercise training and management of risk factors including lipids, hypertension, diabetes, smoking and weight.[7] The expected longterm outcome from addressing these core components are detailed in Table 18.4.

Phase	*Time frame*	*Action*
I	During hospital admission and certainly before discharge from hospital	• Assessment of physical, psychological and social needs for cardiac rehabilitation • Negotiation of a written individual plan for meeting these identified needs (given to both patient and general practitioner) • Initial advice on lifestyle, e.g. smoking cessation, physical activity (including sexual activity), diet, alcohol consumption and employment • Prescription of effective medication and education about its use, benefits and harms • Involvement of relevant informal carer(s) • Provision of information about cardiac support groups • Provision of locally relevant written information about cardiac rehabilitation
II	Early post-discharge period	• Comprehensive assessment of cardiac risk, including physical, psychological and social needs for cardiac rehabilitation, and a review of the initial plan for meeting these needs • Provision of lifestyle advice and psychological interventions according to the agreed plan from relevant trained therapists who have access to cardiologist support • Maintain involvement of relevant informal carer(s) • Review involvement with cardiac support groups • Offer resuscitation training for family members
III	4 weeks after an acute cardiac event	As for phase 2, plus: • Structured exercise sessions to meet the assessed needs • Maintain access to relevant advice and support from people trained to offer advice about exercise, relaxation, psychological interventions, health promotion and vocational advice
IV	Longterm maintenance of changed behavior	• Longterm follow-up in primary care • Offer involvement with local cardiac support groups • Referral to specialist cardiac, behavioral (e.g. exercise, smoking cessation) or psychological services as clinically indicated

Adapted from The National Service Framework for Coronary Heart Disease, 2000.[8]

Table 18.3
Four phases of cardiac rehabilitation.

Component	*Expected longterm outcome*
Psychological management (may include use of psychotropic medication)	• Evidence of emotional wellbeing indicated by the absence of clinically significant psychological distress, social isolation, or drug dependency • Demonstration of self-responsibility for health-related behavior change: – relaxation and other stress management skills – ability to obtain effective social support – compliance with use of psychotropic medications, if prescribed – reduction or elimination of alcohol, tobacco, caffeine, or other nonprescription psychoactive drugs • Develop a plan for ongoing management if important psychosocial issues are present
Lipid management	• LDL <2.6 mmol/L (100 mg/dL) • HDL >0.9 mmol/L (35 mg/dL) • Triglyceride 2.3 mmol/L (<200 mg/dL)
Hypertension management	• BP <130 mm Hg systolic and <85 mm Hg diastolic
Diabetes management	• Fasting plasma glucose in normal range <7 mmol/L (80–110 mg/dL) or HbA_1C <7% • Minimization of complications • Control of associated hyperlipidemia, obesity, hypertension
Smoking cessation	• Complete abstinence from smoking and use of all tobacco products at 12 months from quit date
Weight management	• Adherence to diet and exercise program aimed toward established target weight
Nutritional counseling	• Adherence to prescribed diet • Understanding of basic dietary principles, including calories, saturated fat, cholesterol and other nutrients • Plan in place to address eating behavior problems
Physical activity counseling	• Increased participation in domestic, occupational and recreational activities • Improved psychosocial wellbeing, reduction in stress, facilitation of functional independence, prevention of disability and enhancement of opportunities for independent self-care to achieve recommended goals
Exercise training	• As a component of an overall program of cardiac rehabilitation/secondary prevention, exercise will assist in lowering cardiovascular risk and improve overall outcomes. Improved functional capacity through enhanced muscular endurance and strength, flexibility, and weight management will improve symptoms and physiological responses to physical challenges and should assist in the modification of various unhealthy behavioral and psychosocial characteristics • Patient understanding of safety issues during exercise

Adapted from Core Components of Cardiac Rehabilitation/Secondary Prevention Programs.[7]

Table 18.4
Expected longterm outcome of cardiac rehabilitation.

Current provision

Evidence from two audits has suggested room for improvement in provision in the UK.[58,59] There was poor adherence to published guidelines with respect to content and delivery of cardiac rehabilitation. Staff involvement was mainly limited to nurses, dieticians and physiotherapists with under-representation of physicians, psychologists, occupational therapists, social workers and vocational counsellors. Blood pressure and lipid measurements were commonly recorded (about three quarters of centers) although figures obtained were not always up-to-date and were not necessarily reassessed to establish ideal goal attainment. Fewer centers provided a validated assessment of weight, diet, smoking, anxiety and depression, stress, sleep or sexual functioning. As is commonly found, only a small majority of eligible patients attended cardiac rehabilitation and some patients were excluded by age limitations on some programs. Although core components, such as exercise training, relaxation and education, were included in many programs, this was not always at a beneficial level. Reassessment of current provision should reveal improvement. Adherence to published guidelines should eliminate intercenter variation and should ensure that interventions are delivered at a beneficial level.

Cost effectiveness

Cost analysis of cardiac rehabilitation is difficult because of the heterogeneous nature of program content, staff involvement, patient population and uptake and/or adherence. This is confirmed by the results of a study of 25 randomly selected courses in England and Wales that attempted to estimate the average annual staff running cost per center, per patient/per session and per patient completing the program (Table 18.5).[60] Cost variation between centers was related to the number of patients who used the service and length of staff contact time per patient.

Detailed data on running costs must be combined with data on the effectiveness of cardiac rehabilitation in order to establish

Staff costs over one year	*Mean (SD) (£)*	*Median (£)*	*Range (£)*
Total staff costs	32 887 (13 214) $47 028 ($18 896)	31 692 $45 320	10 238–61 854 $14 640–$97 031
Per patient	371 (436) $530 ($623)	223 $319	66–1433 $94–$2049
Per patient/session	47 (56) $67 ($80)	26 $37	5–179 $7–$256

(£ = US$1.43)
Adapted from Gray AM et al, 1997.[60]

Table 18.5
Staff costs over one year for 16 centers in England and Wales (1997).

Measure of cost	*Cardiac rehabilitation (£)*	*Other cardiovascular interventions (£)*	
Cost effectiveness (£/life year gained)	15 700	Smoking cessation	600
		Aspirin	1600
		Beta-blockers	2800
		Statins	38 300
		Ace inhibitors	54 300
Cost utility (£/quality adjusted life year gained)	6900	CABG (single vessel and mild angina)	35 800
		CABG (left main)	4100
		Treatment of diastolic hypertension	
		Mild	18 200
		Severe	9300

Adapted from Taylor and Kirby, 1997,[57] with figures based on study by Oldridge et al, 1993.[56]

Table 18.6
Cost of cardiac rehabilitation compared with other cardiovascular interventions.

aspects of cost effectiveness. One US randomized controlled trial of cardiac rehabilitation included a detailed cost analysis.[61] Data from this study has been extrapolated and applied to reflect possible UK costs (Table 18.6).[62]

In two trials with extended follow-up, cardiac rehabilitation participants were less likely to utilize health services, be hospitalized for CAD and were more likely to return to work earlier than non-participants.[63,64] Earlier return to work resulted in a saving of £8097 ($11 578) per patient, with a £448 ($641) saving for reduced healthcare utilization during a 5-year follow-up and a £338 ($483) saving for reduced CAD admissions over 3 years. A median cost per participant per year of £223 ($319) would thus be recouped by about the third year.[62]

Although cost analysis of cardiac rehabilitation appears favorable, figures are based on non-UK studies. In addition, the two trials mentioned above were not randomized and so results should be treated with some caution. The running costs of UK programs have been shown to vary widely and although standardized delivery of cardiac rehabilitation may help to smooth out variation in delivery costs, in practice this may not be realized in the immediate future. Information on delivery costs should be coupled with carefully calculated costs of benefit in order to determine an accurate picture of differing aspects of cost effectiveness.

Attendance rates

Despite the potential benefits of structured intervention, many patients either decline to attend (uptake ranges approximately 20–65%) or demonstrate poor adherence to courses. Non-attendance may be a result of referral failure or attendance failure. Those who are referred but do not attend are likely to be older, have lower income/greater deprivation, deny their illness and are less likely to believe that they can influence the course and outcome of their illness. Job status, gender and

health concerns play an indirect role in attendance behavior. The perceived strength of physician recommendation independently influences attendance[65] and it is important that clinicians realize this.

In the elderly there is evidence that both attendance and referral failure influence participation. A gender referral bias in elderly patients,[23] and an age bias against patients aged 75 or older (despite no reported contraindication to attendance)[66] have been reported. Even when there is no evidence of referral failure, older age is consistently associated with non-attendance.[65,67–69] It has been suggested that increased depression in patients aged 65 years or older who are discharged from hospital with a cardiac diagnosis could be an explanation for age-related attendance bias,[70] although this and other possible explanations should be further explored.

Although structured programs have been shown to be of equal benefit to both sexes,[20,22] women may be less likely to attend cardiac rehabilitation. Attendance failure may result from gender specific barriers and/or differences in the perception of coronary heart disease and its treatment between men and women following MI, CABG and PTCA.[68] Within gender, there may be cultural differences. There is a paucity of data regarding cardiac rehabilitation attendance amongst different ethnic groups, although trends in CHD have been shown to vary widely according to ethnic group.[71] In the US, occurrence of, and mortality from CHD are higher among middle-aged black men than native Americans, Asians or hispanic groups. Non-hispanic whites also have relatively high CHD mortality.[71] However, mortality rates are declining more slowly in black men and access to healthcare and patterns of health behavior have been shown to differ according to ethnic group, with blacks and hispanics being less likely to report participation in leisure-time physical activity.[72] It would appear that being currently married positively influences participation, but married men are more likely to attend than married women. Social support confers a positive effect on psychological adjustment and recovery in patients with coronary heart disease,[73] and the encouragement by a spouse to adhere to treatment advice may be one mechanism by which social support operates. Married women may find a conflict between family responsibilities and cardiac rehabilitation participation and course organizers should be aware of this.

Patients with a lower socio-economic status (blue collar vs white collar worker)[65] and greater social deprivation[74] are also less likely to participate. Level of education and low income may influence attendance rates through misconceptions about the illness, attitudes towards benefits and barriers to attendance.[75] Sociodemographic variables can identify who may be less likely to attend but will not provide insight as to why these patients are less likely to attend. Such characteristics are fixed and cannot be altered in order to promote attendance. In contrast, psychological variables associated with attendance, such as beliefs about illness or specific treatment, may be amenable to change. This provides a rationale for the development and testing of psychological interventions.

Patients who feel they have some degree of personal control over the course of their illness whilst hospitalized for MI or CABG are more likely to attend cardiac rehabilitation.[44,67] Similarly, patients' views regarding their fitness and exercise capability may also influence

attendance. Regular exercisers are more likely to attend than patients who perceive themselves as being mildly rather than moderately physically impaired.[76] Patients' views about the content of cardiac rehabilitation programs and their concerns about exercising could be further explored.

It is pertinent that it may be the most vulnerable who fail to attend cardiac rehabilitation: patients who are less physically active, the elderly, women (who may have a worse risk factor profile)[77,78] and those on a low income or who are socially deprived. These patients may have the most to gain from vigorous secondary prevention and it is important that barriers to attendance in these groups are clearly identified and challenged.

Conclusion

Cardiac rehabilitation should be perceived by healthcare professionals responsible for the care of patients with coronary heart disease as a longterm process, which begins during hospitalization and continues thereafter. The more structured intervention program offered to patients is just one part of their overall rehabilitative care, although the extent to which a patient feels a structured program is endorsed and recommended by their physicians will influence their decision to attend and it is important that physicians realize this.

There is an increasing evidence base for the clinical benefit of a multidisciplinary approach to cardiac rehabilitation. Guidelines should therefore be implemented in order to produce unity of provision between centers. This will further enable the cost benefit and cost effectiveness to be determined.

With regard to provision of structured courses, there is a changing focus within the cardiac rehabilitation arena, from provision and recommendation of structured, standardized programs, to recognizing the need for individually tailored prescriptions of effective evidence-based interventions. Such interventions may continue to be delivered through a structured program, but require flexibility and interaction between disciplines, both in hospital and in primary care.

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19

New Thoughts in Antiarrhythmic Therapy

Peter A O'Callaghan and A John Camm

Introduction

Major advances in our understanding and management of cardiac arrhythmias have taken place over the last decade. Radiofrequency catheter ablation has dramatically altered the management of non-life threatening tachycardias and implantable defibrillators have become first-line therapy in the management of cardiac arrest survivors. In high-risk patients who have not previously experienced a life-threatening ventricular tachyarrhythmia, primary prevention of sudden death has been the focus of major prospective multicenter clinical trials. The role of device therapy and prophylactic drug therapy in these patients has yet to be fully elucidated (Table 19.1).[1–9]

Several strategies, both competing and complementary, are frequently available to the clinician. This chapter will give a brief overview of the management of cardiac arrhythmias and focus on the present role of drug therapy, both as monotherapy and in combination with non-pharmacologic options.

Multidimensional approach to arrhythmia management

Antiarrhythmic therapy has traditionally focussed on either prevention of the tachycardia or terminating the episode once tachycardia has occurred. In prevention, typical approaches have included altering the electrophysiologic properties of the substrate (e.g. prevent re-entry by slowing/blocking conduction or by prolonging repolarization), suppressing ectopic activity, decreasing cardiac sympathetic activation, and pacing to prevent pauses. In termination, typical approaches include antiarrhythmic drugs and implantable devices.[10–13] These 'downstream' therapies (Fig. 19.1) do not suppress the tachycardia permanently, but modify transiently the substrate which is the cause of the tachycardia, and therefore accomplish little other than to increase the arrhythmia-free interval.

Ideally tachycardias should be managed either by abolishing the arrhythmic substrate in patients who have experienced spontaneous events, or by preventing development of the arrhythmic substrate in patients at risk of future events. Major advances in 'upstream' management of arrhythmias have occurred in the last decade (see Fig. 19.1) and have resulted in new therapeutic and preventative strategies. In general, if a small volume of cardiac tissue forms a critical part of the arrhythmia mechanism, the tachycardia can be permanently cured by radiofrequency catheter ablation. Accessory pathway-mediated tachycardias and AV node re-entrant tachycardia (AVNRT) are routinely ablated in

Trial	*Type*	*Study population*	*Treatment groups*	*Result*
CAST[1] 1991	Primary prevention	n = 1498 post MI, ≥6 VPBs/Hr and suppressed by trial drug	flecainide or encainide vs placebo	Excess mortality in drug treated (Class I_c) patients
ESVEM[2] 1993	Secondary prophylaxis	documented VT, VF or syncope plus both ≥10 VPBs/Hr and inducible VT/VF	sotalol vs six Class I agents	Sotalol resulted in significantly lower total mortality and arrhythmic mortality than Class I agents
CHF-STAT[3] 1995	Primary prevention	n = 674 Chronic symptomatic HF ≥10 VPBs/Hr, LVEF ≤0.40	amiodarone vs placebo	Amiodarone did not prolong survival or reduce the incidence of sudden death
MADIT[4] 1996	Primary prevention	post MI with LVEF ≤0.35, NSVT and inducible, nonsuppressible VT or VF	ICD vs conventional medical therapy	Terminated due to significantly fewer deaths in ICD group
SWORD[5] 1996	Primary prevention	n = 3121 post MI with LVEF ≤0.40	d-sotalol vs placebo	Terminated due to excess arrhythmic mortality in patients treated with d-sotalol
US Carvedilol Heart Failure Trial[6] 1996	Heart failure study	n = 1094 chronic symptomatic HF LVEF ≤0.35	carvedilol vs placebo	Terminated due to large decrease in risk of dying of either progressive heart failure or sudden death
AVID[7] 1997	Secondary prophylaxis	n = 1016 cardiac arrest survivors or VT with either syncope or hypotension + LVEF ≤ 0.40	ICD vs amiodarone or guided sotatol therapy	The ICD is superior to antiarrhythmic drug therapy for increasing overall survival
EMIAT[8] 1997	Primary prevention	n = 1486 post MI, LVEF ≤0.40	amiodarone vs placebo	Amiodarone did not prolong overall survival but reduced the number of arrhythmic deaths
MUSTT[9] 1999	Primary prevention	n = 704 coronary artery disease, LVEF ≤0.40, NSVT	EP-guided therapy vs no antiarrhythmic therapy (controls)	EP-guided therapy, in particular ICD therapy, significantly reduced the risk of cardiac arrest and arrhythmic death

Table 19.1
Major trials on the role of antiarrhythmic drug therapy in tachyarrhythmias.

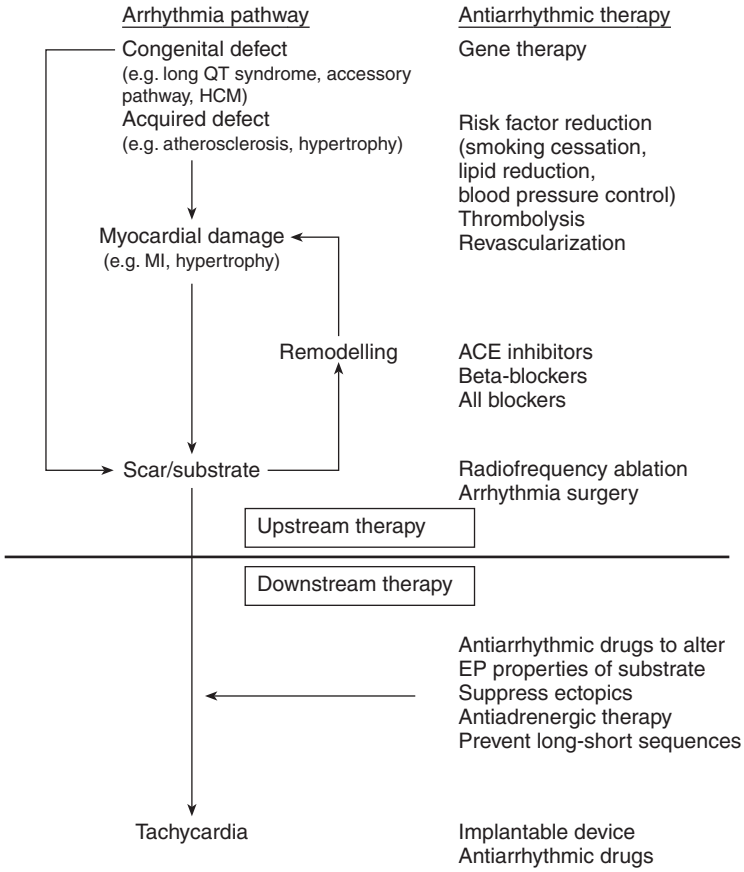

Figure 19.1
The arrhythmic pathway, from congenital or acquired defect to tachycardia expression, and potential targets for antiarrhythmic therapy. Therapy targetted at preventing or reversing the development of arrhythmic substrate is 'upstream' therapy; therapy targetted at tachycardia expression and termination is 'downstream' therapy.

most centers with success rates greater than 90%.[14] Targetted ablation is increasingly being used in conditions such as atrial tachycardia, right ventricular outflow tract and idiopathic left ventricular (LV) tachycardias, and bundle branch re-entrant tachycardia.

Even macrore-entrant tachycardias are now successfully ablated because of a greater understanding of the electrophysiologic mechanisms and improved technology in mapping and catheter ablation. Atrial flutter, a macrore-entrant tachycardia with a circuit bounded anteriorly by the tricuspid annulus and posteriorly by the crista terminalis, is now

curable by creating a continuous line of electrical block between the tricuspid valve and the inferior vena cava. This anatomical approach, the endpoint of which is the creation of bidirectional isthmus block, is proving effective in over 80% of patients undergoing ablation.[15] For years, atrial fibrillation was thought to require the creation of multiple lines of electrical block (surgical or catheter-based Maze procedure) to prevent multiple wavelets of re-entry. In a subset of patients, it is now known to be either triggered or maintained by a rapidly firing focus, usually located within the pulmonary veins, and is amenable to focal ablation.[16]

Moving further upstream, an integral part of the management of ventricular tachyarrhythmias (ventricular tachycardia and ventricular fibrillation) should include revascularization in patients with obstructive coronary artery disease and aggressive treatment of heart failure in patients with dilated cardiomyopathy. Thrombolysis and revascularization by limiting the infarct size will reduce the amount of scar tissue, and prevent the development of LV aneurysms which commonly result in sustained monomorphic ventricular tachycardia. Transient ischemia is also suspected as a major trigger for life-threatening ventricular tachyarrhythmias and carefully selected patients require revascularization rather than antiarrhythmic therapy.[17] Pharmacologic agents, including angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonists and beta-blockers which prevent or reverse ventricular remodelling may not only prevent progressive heart failure but may also favorably influence the arrhythmic substrate and reduce the incidence of sudden death.

When sudden cardiac death (SCD) is measured as an absolute number of events, it becomes clear that patients at highest risk (e.g. cardiac arrest survivors, individuals with poor ejection fraction) do not account for the majority of SCD victims. Large population subgroups, at low individual risk, generate the largest absolute number of SCD events as a result of the large size of the population pools in which the events occur. Therefore, the long-term strategy most likely to reduce the incidence of SCD is the prevention of acquired heart disease by effective risk factor management strategies (smoking cessation, lipid management, hypertension control).

Major advances in our understanding of the genetics of congenital long QT syndrome and hypertrophic cardiomyopathy have been made in recent years. For example, in congenital long QT syndrome, optimal therapy may depend on the specific genetic defect. Long QT syndromes linked to chromosome 3 (LQT3) may respond better to mexiletine whereas long QT syndromes linked to chromosome 2 (LQT2) may respond better to beta-blockade.[18] In the future, genetic profiling and gene-specific therapy may become the ultimate 'upstream' therapy in the management of cardiac arrhythmias.

In summary, antiarrhythmic drug therapy must be assessed in the context of the 'holistic' approach outlined above, with reference to alternative therapies available. The remainder of this chapter will focus on the role of antiarrhythmic drug therapy in the symptomatic management of tachycardias, secondary prevention of life-threatening ventricular tachyarrhythmias, and primary prevention of sudden death. The increasing role of antiarrhythmic drug and device therapy in combination with other available treatment strategies will also be reviewed. Antiarrhythmic drugs

Class	*Mechanism of action*	*Drug*
I	**Na channel blockade**	
IA	+ prolong repolarization	quinidine, procainamide and disopyramide
IB	+ accelerate repolarization	mexiletine, lidocaine, and phenytoin
IC	+ marked conduction slowing	flecainide, encainide, propafenone and moricizine
II	**Sympatholytic agents**	**beta-blockers**
III	**Prolong repolarization**	
'Conventional' class III agents	I_{KR} channel blocker and beta-blocker multiple complex channel blocking and antiadrenergic properties	sotalol amiodarone
'Pure' class III agents	Prolong repolarization without other pharmacologic effects	d-sotalol, dofetilide, sematilide, ibutilide, and azimilide
Class IV	**calcium channel antagonists**	**calcium channel blockers**

Based on the Vaughan Williams classification.

Table 19.2
Classification of antiarrhythmic drugs.

are conventionally classified according to their predominant electrophysiologic mechanism of action (Table 19.2). Although this is a simplistic approach, and drugs within the same subclass may have important differences, it forms a useful framework for considering appropriate drug options.

Symptomatic management of tachycardias

Treatment goals and options

Symptomatic relief is the principal aim of management in patients who do not have life-threatening tachyarrhythmias. Drug therapy in many individuals does not result in complete abolition of the arrhythmia but is nevertheless successful if it results in substantially fewer and better tolerated events. It is difficult to assess the success rate of antiarrhythmic drug therapy in the management of arrhythmias. Studies have employed different outcome measures, usually involved small sample sizes, and have inadequately defined the arrhythmia mechanisms. For example, both AV node reentry tachycardia (AVNRT), which utilizes dual AV nodal pathways, and AV reciprocating tachycardia (AVRT), which utilizes an accessory pathway, are frequently combined

together under the term supraventricular tachycardia (SVT). Antiarrhythmic drug therapy is usually efficacious in 70–90% of SVT patients.[14] However, up to 50% of these patients have unwanted side-effects. Therefore in only 35–45% of all patients will a chosen agent be both effective and well tolerated and hence a satisfactory long-term option for the patient. In the remaining group of patients not only alternative drug options but also non-pharmacologic options need to be considered in deciding further therapy.

Patients with arrhythmias such as AVNRT or AVRT which can be easily ablated (95% + success rates) are, in our institution, routinely offered a radiofrequency catheter ablation if they have failed one trial of antiarrhythmic drug therapy. In contrast, patients with arrhythmias such as atrial tachycardia or atrial flutter where acute success rates of catheter ablation are approximately 80% or less are frequently offered a variety of antiarrhythmic agents before a decision is taken to proceed to radiofrequency ablation.

Management options in atrial fibrillation, which until recently consisted of maintaining sinus rhythm versus ventricular rate control, have in recent years expanded to include the 'ablate and pace' strategy, Maze surgery, focal atrial fibrillation ablation, AV node modification or implantation of an atrial defibrillator (Table 19.3). The approach employed for a given patient, whether pharmacologic or non-pharmacologic or a combination of both, needs to be individualized, if necessary, in consultation with a cardiac electrophysiologist.

Symptomatology

Other factors apart from the arrhythmia substrate which need to be considered in deciding the most appropriate treatment for an individual patient are symptomatology and underlying structural heart disease. Patients with infrequent episodes of palpitations may, after appropriate investigation and diagnosis, simply be reassured as to the benign nature of their arrhythmia or offered a 'pill in the pocket' approach. Patients with frequent troublesome palpitations may undergo trials of antiarrhythmic therapy in an attempt to find a well-tolerated efficacious agent or may be offered a non-pharmacologic option as discussed above. Patients who experience syncope associated with palpitations are usually offered a diagnostic electrophysiologic study followed, if necessary, by radiofrequency ablation rather than drug therapy.

Present
AV node ablation and pacemaker implantation
Surgical Maze
Focal AF ablation
AV node modification
Atrial defibrillator
Future
Catheter percutaneous Maze procedure
Radiofrequency modified Maze surgery
Pulmonary Vein Isolation
Pacemaker therapy (single-site, dual-site atrial pacing)

Table 19.3
Non-pharmacologic options in management of atrial fibrillation.

Proarrhythmia risks

Since the early 1990s, there has been a fundamental change in our approach to antiarrhythmic drug therapy for the symptomatic treatment of tachycardias. Patient safety is now the main factor determining the choice of antiarrhythmic therapy and proarrhythmic risks need to be carefully assessed prior to initiating therapy.[19] The Cardiac Arrhythmia Suppression Trials (CAST) randomized recent myocardial infarction survivors with spontaneous and suppressible ventricular ectopy either to therapy with a Class I_C drug (flecainide, encainide or moricizine) or to placebo. CAST was stopped prematurely when mortality among patients receiving flecainide or encainide was found to be two- to three-fold higher than in patients receiving placebo.[1] The results of CAST caused major concern because excess mortality was not due to early drug proarrhythmia. The combined incidence of death and non-fatal ischemia was the same for the drug and placebo arms of CAST, but the active drug resulted in the conversion of more ischemic and heart failure episodes into fatal events throughout the entire follow-up period.[20]

Subgroup analysis of the CAST data revealed that patients exposed to active drug with non-Q wave myocardial infarction (MI) (a group at high risk of recurrent myocardial ischemia) were at 8.7 fold increased risk of death, compared to a 1.7 fold increased risk of death among those who had a transmural (Q wave) MI.[21] These findings are supported by animal studies which found that acute myocardial ischemia in the presence of a sodium channel blocking agent increases the incidence of ventricular fibrillation.[22] As a result, class I_C drugs are now absolutely contraindicated in patients with coronary artery disease and many physicians avoid these drugs in any patient with structural heart disease of any sort. Prior to commencing a I_C agent, it is necessary to exclude underlying ischemic heart disease using exercise stress testing and cardiac catheterization as indicated.

In addition to the CAST findings, other reports have raised concerns about the use of all Class I agents. Quinidine, which is a known cause of torsade de pointes (quinidine syncope), is associated with increased mortality compared to placebo in patients with atrial fibrillation.[23] In post-MI survivors, mexiletine and disopyramide results in a trend towards increased mortality.[24,25] This has resulted in a shift from Class I to Class III antiarrhythmic agents and extensive ongoing research into the development of new Class III agents without the beta-blocker side-effects of sotalol or the toxic extracardiac side-effects of amiodarone.

In order to administer antiarrhythmic agents as safely as possible, it is helpful to be familiar with the different proarrhythmia mechanisms and their main predisposing risk factors (Table 19.4).[19] Consideration of the proarrhythmic risk will help to determine which agent is safest and most appropriate, the level of monitoring required at the time of drug initiation, and whether a non-pharmacologic option would carry less risk to the patient. Patients with structurally normal hearts and normal QT intervals, or with implantable defibrillators, are either at very low risk of torsade de pointes and sudden death or are protected from the life-threatening consequences of these proarrhythmic events. In these patients it is possible to persevere with drug therapy until an efficacious, well-tolerated agent is identified.

Proarrhythmia mechanism	*Drug*	*Predisposing risk factors*
'Late' sudden death (arrhythmic mechanism not clearly defined)	Class I_c flecainide, encainide, moricizine, quinidine d-Sotalol	Myocardial ischemia Predominant
Torsade de pointes	Class I_a quinidine, procainamide, disopyramide Sotalol 'Pure' class III d-sotalol, ibutilide, dofetilide	Baseline QT prolongation/dispersion Female gender Hypokalemia/Diuretic use Clinical heart failure Advanced structural heart disease Conversion of AF to sinus rhythm Hypertension/hypertrophy?
Atrial flutter with 1:1 AV conduction and wide QRS complexes	Class I_a quinidine, disopyramide Class I_c flecainide, propafenone	
Incessant slow VT	Class I_c flecainide, propafenone Class I_a quinidine, in high doses	History of sustained monomorphic VT Ventricular scar (e.g. previous MI)

Table 19.4
Mechanisms of drug proarrhythmia, most frequent causative agents and predisposing risk factors.

Minimizing proarrhythmic risk

To select a reasonable drug option, it is first necessary to consider the underlying structural heart disease (Table 19.5). Ventricular proarrhythmia is seen most frequently in patients with substantial LV dysfunction and much more rarely in patients with structurally normal hearts. In the latter patients, no antiarrhythmic class is contraindicated and class I_C agents are commonly chosen as first-line therapy because of their favorable side-effect profile. In patients with coronary artery disease, class I_C agents are absolutely contraindicated and all class I agents need to be administered with caution. Sotalol, which has beta-blocking properties, and amiodarone are reasonable options in patients with coronary artery disease. Patients with left ventricular hypertrophy/hypertension are at increased risk of ventricular arrhythmias and, although data is lacking, are suspected of being at increased risk of torsade de pointes.[26,27] Drugs known to cause torsade de pointes (sotalol and class I_a) should probably be avoided in patients with hypertrophy. Suitable options in this setting include class I_C agents (especially propafenone which has beta-blocking properties) and amio-

Structural heart disease	*Reasonable drug option*	*Avoid or extreme caution*
None	Class I_C all antiarrhythmic agents	None
Coronary artery disease	sotalol amiodarone disopyramide	all Class I_C absolutely contraindicated Class I_a and I_b with caution
Hypertension/hypertrophy	Class I_C (esp propafenone) amiodarone	sotalol Class I_a
History of heart failure	digoxin beta-blocker amiodarone	all Class I agents sotalol

Table 19.5
Antiarrhythmic drugs and underlying heart disease.

darone. Patients with a history of heart failure are at particularly high risk of ventricular proarrhythmia and should be treated with either digoxin, beta-blocking agents or amiodarone.

Once a suitable drug is chosen, the physician must decide whether to initiate therapy as an inpatient or as an outpatient. Class I_a and class III drugs prolong repolarization and have more potent antiarrhythmic effects at slower heart rates (reverse use-dependence). The electrophysiologic effects of these drugs occur at times of bradycardia (at rest and during nighttime) and either QT prolongation or proarrhythmia will usually be seen within the first 3 days of initiating drug therapy (Fig. 19.2). It is therefore reasonable to consider inpatient monitoring when starting these agents. Patients with no structural heart disease, normal QT interval and no sinus node dysfunction or atrioventricular conduction abnormalities are at very low risk and need not be admitted to hospital for initiation of drug therapy.[28] Throughout the maintenance period, ECGs to measure QT intervals and serum potassium should be checked regularly,

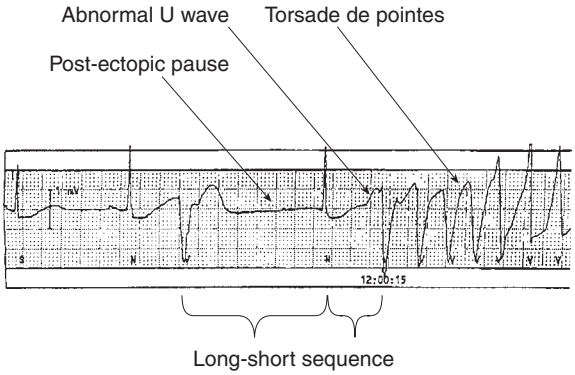

Figure 19.2
Background bradycardia and ectopy, resulting in a long-short sequence and initiation of torsade de pointes. Note pause-dependent QT prolongation and abnormal U wave.

other QT-prolonging drugs should be avoided, and care should be taken when adjusting diuretic medication or adding agents known to cause bradycardia. Class I_C drugs have more potent antiarrhythmic effects at faster heart rates (use-dependence). Therefore it is advisable to perform an exercise stress test on maintenance therapy looking for QRS widening and ventricular proarrhythmia during sinus tachycardia and to outrule underlying myocardial ischemia. There is no evidence to support the need to initiate these drugs in hospital.

In a review of drug therapy for supraventricular tachycardia reported in the literature since 1922, two-thirds of all proarrhythmic episodes were preceded by restoration of sinus rhythm.[29] A typical example is a patient in atrial fibrillation who is given a QT-prolonging drug which results in chemical cardioversion. After restoration of sinus rhythm, bradycardia with atrial premature beats results in a long-short sequence which initiates torsade de pointes. It may be safer to admit patients with persistent atrial fibrillation for elective cardioversion and then commence them on a QT-prolonging drug to maintain sinus rhythm. One possible exception to this is the administration of amiodarone as an outpatient for 6 weeks prior to cardioversion to increase the likelihood of success. This approach is reasonably safe as there is a low risk of torsade de pointes associated with amiodarone. However, this approach may unmask significant sinus node or atrioventricular conduction system disease at the time of cardioversion. Patients with infrequent episodes of tachyarrhythmia are commonly treated with a 'pill in the pocket' approach. It is wise to first assess the safety of this strategy as an inpatient.

A potentially life-threatening form of proarrhythmia associated with drugs which slow conduction (class I) is atrial flutter with 1:1 atrioventricular conduction (see Table 19.4). This is most commonly associated with flecainide and quinidine and is less of a problem with propafenone, probably because propafenone has beta-blocking properties. As a result of slowing of atrial flutter cycle length, or conversion of atrial fibrillation or atrial tachycardia to atrial flutter, 1:1 atrioventricular conduction may occur. This proarrhythmia typically results in a rapid wide complex tachycardia which is often misdiagnosed as sustained monomorphic ventricular tachycardia. To avoid this complication, it is useful to consider combination therapy with both a Class I agent and an atrioventricular nodal slowing agent, such as a calcium channel antagonist, a beta-blocker or digoxin.

Recent large primary prevention trials have focused attention on the additional positive benefits of beta-blockade in the prevention of proarrhythmia.[30] In the CAST trial, patients who received both active antiarrhythmic agent (class I_C) and beta-blocker therapy had significantly better survival than patients who only received flecainide or encainide.[31] This should be interpreted cautiously as beta-blockers were not randomized and these patients may have had less proarrhythmic risk independent of beta-blockade. In the European Myocardial Infarction Amiodarone Trial (EMIAT), mortality among patients treated with both amiodarone and beta-blockers was substantially less than in patients treated with amiodarone alone.[32] Beta-blockers are antiischemic, anti-adrenergic, increase the threshold for ventricular fibrillation, prevent catecholamine reversal of antiarrhythmic drug effects and may have beneficial effects on the

underlying heart disease.[33] It is therefore prudent to consider combining antiarrhythmic drug therapy with beta-blocker therapy, especially in patients with known coronary artery disease.

In summary, when symptomatically treating tachyarrhythmias, patient safety is the predominant factor in guiding the choice of antiarrhythmic therapy. To minimize proarrhythmic risk, it is necessary to consider:

- Underlying structural heart disease
- Whether to start therapy as an inpatient
- Monitoring ECGs, serum potassium and concomitant medication regularly during the maintenance period
- Combination therapy with atrioventricular nodal slowing agents and/or beta-blocker therapy

Secondary prevention of life-threatening ventricular tachyarrhythmias

Pharmacologic therapy

Survivors of cardiac arrest are at high risk of future recurrences, in the absence of acute MI.[34] Therefore the aim of therapy in the management of life-threatening ventricular tachyarrhythmias (ventricular fibrillation and hypotensive ventricular tachycardia) is the prevention of SCD. In the 1980s, empiric antiarrhythmic drug therapy was replaced by guided drug therapy, using either invasive electrophysiologic (EP) drug testing or non-invasive electrocardiographic monitoring. Unfortunately, guided approaches did not live up to their initial expectations. The majority of patients with life-threatening ventricular tachyarrhythmias are either not suppressed by EP-guided drug therapy or are not inducible at baseline EP study.[35,36] In patients with poor left ventricular ejection fraction (LVEF $< 30\%$) or with substrates other than chronic coronary atherosclerosis, guided drug therapy does not accurately predict efficacy.[35,37,38] More importantly, the sudden death rate in patients whose ventricular tachyarrhythmias are suppressed by EP-guided drug therapy is higher than in patients who undergo ICD implantation.[2,13,39–41]

As a result, guided drug therapy is no longer accepted as first line therapy in the management of life-threatening ventricular tachyarrhythmias. The only drug therapy that has challenged the superiority of implantable defibrillators in the management of life-threatening ventricular tachyarrhythmias has been empiric amiodarone therapy.[42] In patients with preserved left ventricular systolic function, empiric amiodarone therapy and device therapy have been shown to result in similar long-term survival.[43]

Device therapy

As a therapeutic modality, the implantable cardioverter defibrillator (ICD) is unsurpassed in its ability to prevent SCD (Fig. 19.3).[44] However some investigators have argued that total mortality is not reduced when compared with the best available medical therapy. Although sudden death is markedly reduced, overall mortality in ICD recipients reaches 20% at 2 years in some studies and is a function of the severity of underlying heart disease.[44] In patients with heart failure, there was a concern that implantable defibrillators may have little effect on overall survival for several reasons. Firstly, as NYHA functional

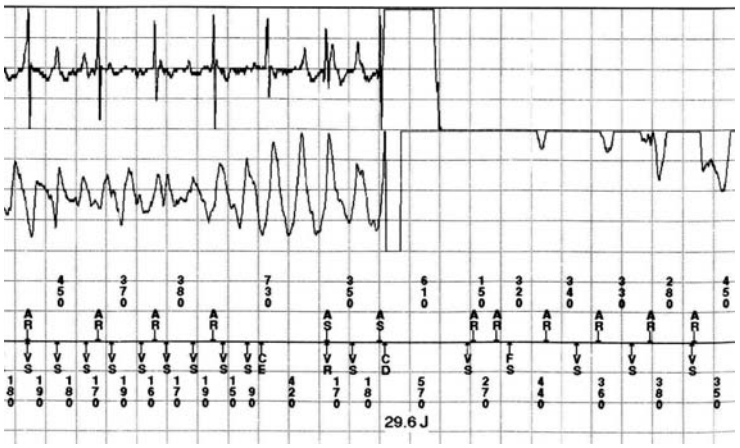

Figure 19.3
Stored electrograms of successful defibrillation of ventricular fibrillation. The recording is a continuous strip consisting of a waveform channel and a status channel. The detection criteria of the device are met (VF = 320 ms) and a high voltage biphasic shock (29.6 J) is delivered after 11 sec. A rectangular deflection marker on the channels denotes it. The high voltage shock restores sinus rhythm. AR, atrial sensing (during refractory period), VS,ventricular sensing.

class deteriorates, the proportion of deaths which are sudden and unexpected decreases. Secondly, in advanced heart failure, the proportion of sudden deaths which are due to bradyarrhythmias and electromechanical dissociation becomes substantial, accounting for up to 50% of all sudden deaths in some series.[45,46] These episodes are usually agonal rhythms in patients with severely impaired systolic function and death is not prevented by backup pacing. Finally, successfully terminating an episode of ventricular tachycardia or fibrillation will have little effect on overall survival if the patient dies shortly thereafter of progressive pump failure. Because of these concerns, prospective randomized trials were conducted in recent years to test the hypothesis that implantable defibrillators significantly improve total survival.

The results of two large prospective multicenter trials (AVID and CIDS) that compared implantable defibrillators and amiodarone therapy in patients with life-threatening ventricular tachyarrhythmias have reported that the implantable defibrillator is superior to amiodarone for increasing overall survival.[7,47] In the AVID trial, implantable defibrillators resulted in a 31% reduction in total mortality at 3 years compared to patients treated with amiodarone (Fig. 19.4). Of note, subgroup

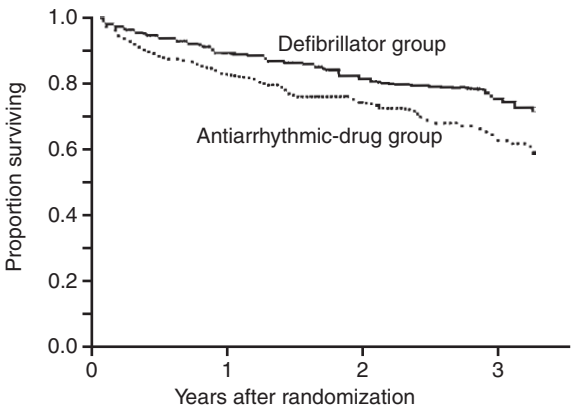

Figure 19.4
Overall survival in the defibrillator group and the antiarrhythmic drug group up to 3 years after randomization in the AVID trial. Survival was better among patients treated with the implantable defibrillator ($p < 0.02$). Data reproduced from the AVID investigators.[7]

analysis suggests that patients with LVEF ≤30% derive a greater survival benefit from defibrillator therapy than patients with LVEF >30%, and that patients with LVEF >35% have similar survival with either empiric amiodarone or device therapy.[43]

American College of Cardiology/American Heart Association guidelines advise ICD therapy in cardiac arrest survivors, patients with spontaneous sustained ventricular tachycardia and patients with syncope of undetermined origin with hypotensive ventricular tachycardia or ventricular fibrillation inducible at EP study.[48] In these clinical circumstances, the ICD is now regarded as the treatment of first choice. The role of antiarrhythmic therapy in these patients is mainly limited to adjunctive therapy in ICD recipients who have other tachyarrhythmias (e.g. atrial fibrillation) or who are receiving frequent shocks and require suppressive drug therapy. Drug trials in patients with ICDs may result in the future development of new safe antiarrhythmic agents.

Primary prevention of sudden cardiac death

The majority of patients at risk of SCD have not previously experienced a sustained ventricular tachyarrhythmia. Since short-term mortality rates (before hospital discharge) associated with out-of-hospital cardiac arrest are in the range 70–85%, it is evident that primary prevention strategies will have the greatest impact on reducing mortality from sudden death.[34,49] In addition to 'upstream' therapy (see Fig. 19.1), clinicians have repeatedly tested the hypothesis that antiarrhythmic drug therapy can be employed in the primary prevention of SCD in patients known to be at high risk of sustained ventricular tachyarrhythmia.

Class I antiarrhythmic agents

Ventricular ectopy is a risk factor for cardiac death after myocardial infarction.[50] CAST tested the hypothesis that in post-MI patients, suppression of ventricular ectopy would improve survival.[1] The CAST results highlighted the dichotomy that may exist between antiarrhythmic action (effective ventricular ectopy suppression) and patient outcome (increased mortality). In keeping with these results, class I antiarrhythmic agents have also been found to increase mortality in patients with prior cardiac arrest, in patients with atrial fibrillation, and in patients with ventricular ectopy independent of recent MI.[51] No class I agent has been found to prolong survival in patients with structural heart disease.

Beta-blocker therapy

In contrast to the negative experience with class I antiarrhythmic agents, beta-blockers as a class consistently reduce mortality in a wide spectrum of cardiac disorders. This is hardly surprising as beta-blockade is anti-ischemic, anti-adrenergic and antifibrillatory. Beta-blocker therapy has been shown in many randomized trials to prevent sudden cardiac death in post-MI patients.[52] The Beta-blocker Heart Attack Trial (BHAT) was a prospective randomized, trial of propranolol versus placebo in 3837 patients with recent MI.[10] In this study, treatment with propranolol resulted in a 27% reduction in total mortality and a 28% reduction in sudden cardiac death. Carvedilol is a non-selective beta-1- and beta-2-receptor

blocker, and an alpha-1-blocker (hence a vasodilator) which selectively lowers coronary sinus norepinephrine levels and does not increase the density of cardiac beta-receptors.[53] The US Carvedilol Heart Failure Study Group reported that in mild to moderate heart failure, carvedilol was associated with a large reduction in the risk of dying of both progressive heart failure and SCD.[6] The Cardiac Insufficiency Bisoprolol Study (CIBIS II), which enrolled 2647 patients with New York Heart Association (NYHA) class III or IV heart failure, reported that all cause mortality was significantly lower with bisoprolol than with placebo (11.8% versus 17.3%, $p < 0.0001$).[54] These results are supported by a meta-analysis which found that beta-blockade significantly reduced all cause mortality in patients with heart failure (odds ratio 0.69, 95% confidence interval 0.54–0.88).[55]

Class III antiarrhythmic agents

Much attention has focused in recent years on the primary prevention of SCD in patients with heart failure using amiodarone therapy. Published results include those for prospective randomized trials in patients with heart failure (GESICA and CHF-STAT) and post-MI (EMIAT and CAMIAT), as well as a meta-analysis of amiodarone trials.[3,8,56–58] Based on these trials, a number of conclusions can be drawn. Firstly, prophylactic amiodarone therapy in all patients with LV dysfunction is not justified in terms of risk versus benefit. Secondly, amiodarone appears safe with little or no associated increase in mortality, and a low risk of proarrhythmia in patients with significant structural heart disease. Thirdly, the combination of amiodarone and beta-blocker therapy has synergistic effects with respect to their ability to suppress arrhythmias and prevent SCD.[32]

In patients with LV dysfunction, the absolute risk of sudden tachyarrhythmic death is much less than in cardiac arrest survivors. In this setting, adverse drug side-effects may increase the number of non-arrhythmic deaths (e.g. increased deaths from pump failure, bradyarrhythmias, or pulmonary fibrosis) such that the overall mortality is unchanged, as seen in the EMIAT trial (Fig. 19.5). This 'conversion hypothesis' needs further elucidation.

Ongoing trials such as the SCD in heart failure (SCD-HeFT) trial which is randomizing 2500 patients with dilated cardiomyopathy, ejection fraction ≤35%, and NYHA class II or III heart failure to either conventional therapy, amiodarone or ICD therapy will determine

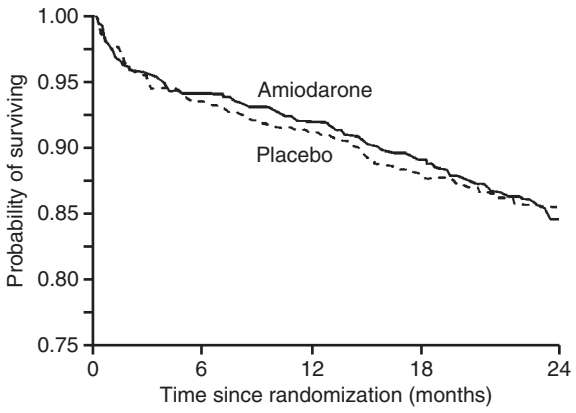

Figure 19.5
Mortality rates in the EMIAT trial. All-cause mortality did not differ between placebo and amiodarone-treated patients. Median follow-up was 21 months. Data reproduced from Julian et al.[8]

how these patients will be managed in the future.[59]

Trials of 'pure' class III antiarrhythmic agents which selectively block the fast component of the delayed rectifier potassium current (I_{Kr}) have to date shown disappointing results in the prevention of sudden death. The Survival With ORal D-sotalol (SWORD) primary prevention trial of 3121 post-MI survivors with LVEF ≤40% was terminated early due to excess mortality in patients treated with d-sotalol.[5] The Danish Investigation of Arrhythmias and Mortality ON Dofetilide (DIAMOND) studies tested the efficacy of dofetilide, a selective inhibitor of I_{Kr}, in high risk patients with recent myocardial infarction or with congestive heart failure.[60] Preliminary data indicate that dofetilide had no impact on total survival in either group of patients.

Future drug trials

Despite the disappointing results of most antiarrhythmic primary prevention trials, important lessons have been learnt which can be used in the design of future drug trials.[61] If antiarrhythmic drugs are administered to a group of patients at too low a risk of sudden death, the potential for benefit is small and may be outweighed by the risks of drug proarrhythmia and nonarrhythmic drug toxicity. In CAST, annual mortality rates in the placebo group was only 3%.[1] Future primary prevention drug trials need to target populations of patients at high risk of arrhythmic death. Low-risk patients who only have a potential for drug proarrhythmia, should be excluded, as well as those at high risk of non-arrhythmic death, such as patients with very severely impaired systolic function. Analysis of CAST, SWORD and EMIAT studies suggests that patients within 1 year of MI, with LVEF 15–35% and with low heart rate variability are at greatest risk of SCD.[61] These data have been employed in the design of the AzimiLide post-Infarct surVival Evaluation (ALIVE) trial.[62] In this trial, patients are treated with either azimilide, a novel non-selective blocker of both the fast and slow components of the delayed rectifier potassium current (I_{Kr} and I_{Ks}), or placebo. Treatment commenced within 21 days of MI and has been administered for one year only to post-infarct patients with LVEF 15–35%.[62]

The implantable defibrillator and primary prevention

With the exception of beta-blocker therapy, all other antiarrhythmic agents tested to date have failed to show consistent benefit in the prevention of SCD. In contrast, in a highly select group of patients' prophylactic therapy with an ICD has been shown to improve survival compared to conventional medical therapy. In the Multicenter Automatic Defibrillator Implantation Trial (MADIT), patients with prior MI, ejection fraction ≤35%, non-sustained ventricular tachycardia and inducible, non-suppressible ventricular tachyarrhythmia on invasive electrophysiologic testing received either prophylactic ICD implantation or conventional medical therapy.[4] During a mean follow-up of 27 months, the mortality rate was 15.8% in the ICD group compared to 38.6% in the conventional therapy group ($p < 0.01$).

The Multicenter UnSustained Tachycardia Trial (MUSTT) tested the hypothesis that invasive EP-guided therapy can reduce the risk of sudden cardiac death and cardiac arrest in patients with coronary artery disease, left

ventricular dysfunction (LVEF ≤40%) and spontaneous non-sustained ventricular tachycardia (NSVT).[9] Over 2,000 patients were enrolled, of which approximately one third had inducible sustained ventricular tachyarrhythmia on EP testing. These patients were assigned to either EP-guided therapy or no antiarrhythmic therapy (control group). Patients assigned to EP-guided therapy underwent serial drug testing. Implantation of an ICD could be recommended after at least one unsuccessful drug test. Approximately half of the EP-guided therapy group were discharged on antiarrhythmic drug therapy and half were given ICDs.

MUSTT reported that EP-guided therapy significantly reduced the risk of cardiac arrest and arrhythmic death over 5 years follow-up (27% reduction). However subgroup analysis was of much more importance in the interpretation of the results. All the improvement in the EP-guided therapy group was the result of defibrillator therapy. The overall mortality rate at 5 years was 55% among EP-guided antiarrhythmic drug therapy patients and 48% in the control group. Five-year mortality was significantly less among the EP-guided patients who received defibrillator therapy (24% reduction). The results of MUSTT need to be interpreted with some caution in view of the fact that patients were not randomized between antiarrhythmic drug therapy and defibrillator therapy. However, together with the results of MADIT, the results provide a strong argument in favour of ICD therapy in these patients.

It is possible that ICD therapy only appears superior to prophylactic antiarrhythmic drug therapy due to poor patient selection and poor choice of antiarrhythmic agents in previous trials. The search for novel safe antiarrhythmic agents and better means of risk stratifying patients should continue until we can offer safe, well tolerated antiarrhythmic drugs to patients at risk of sudden cardiac death.

Combination therapy

Antiarrhythmic drug therapy has traditionally been considered in terms of stand-alone therapy. This misconception has been artificially strengthened by clinical trials that compare drug versus device therapy. In practice, optimal management in many patients requires combination or 'hybrid' therapy.

Patients with ICDs commonly require additional antiarrhythmic drug therapy. In most series, approximately two thirds of ICD patients receive concomitant antiarrhythmic drug therapy, either to suppress ventricular tachyarrhythmias or to treat supraventricular tachyarrhythmias, such as paroxysmal atrial fibrillation.[63] The ICD treats an arrhythmic episode after it occurs, and frequent shock therapy is poorly tolerated by most patients. In addition, driving is prohibited in most countries until 6 months after ICD implantation and for a further 6 months after each ICD discharge.[64] In patients who need to drive, it is usually necessary to prescribe antiarrhythmic drug therapy. Drugs may be employed to suppress tachyarrhythmias, to slow the rate of ventricular tachycardia, thereby increasing the likelihood of successful antitachycardia pacing (ATP), to decrease the defibrillation threshold or to increase the fibrillation threshold. Device therapy provides backup in case of drug-induced bradycardia or ventricular proarrhythmia and protection in the event of breakthrough ventricular fibrillation.[65,66]

New algorithms which employ combinations of drug, device and ablative therapy are at present being developed for the management of paroxysmal atrial fibrillation. Single- or dual-site right atrial pacing with a lower rate limit of 80 to 90 beats per minute has been shown to prolong arrhythmia free intervals significantly in patients with drug refractory paroxysmal atrial fibrillation.[11] Pacing to prevent atrial fibrillation can be combined with antiarrhythmic therapy to increase as much as possible the arrhythmia free interval and control ventricular rate during paroxysms. Antiarrhythmic drug therapy may be employed to convert atrial fibrillation to atrial flutter, followed by radiofrequency flutter ablation and continuation of antiarrhythmic therapy to maintain sinus rhythm.[67]

Conclusions

Major advances in understanding of the role of antiarrhythmic drug therapy in the management of tachyarrhythmias have occurred in recent years (Table 19.6). Antiarrhythmic drug therapy needs to be assessed in the context of ablation and device options. In the symptomatic management of tachycardia, patient safety should be the main factor in determining the choice of antiarrhythmic drug and all reasonable precautions should be employed to minimize the risk of drug proarrhythmia. For the foreseeable future, ICDs will be the therapy of first choice in patients who have experienced a spontaneous episode of life-threatening ventricular tachyarrhythmia with combination drug therapy to optimize patient management. Apart from beta-blocker therapy, antiarrhythmic drugs have to date failed in the primary prevention of SCD. Development of newer antiarrhythmic agents and more careful selection of high-risk patients will more than likely result in drug strategies that prevent SCD. The results of several ongoing clinical trials are eagerly awaited. For the present, the relative safety of available antiarrhythmic drug therapy will depend on the indication for its use, underlying structural heart disease, and careful consideration of alternative treatment strategies.

- Class Ic drugs are contraindicated in patients with structural heart disease and all Class I agents need to be employed with caution
- Beta-blockers consistently decrease total and arrhythmic mortality in a wide spectrum of cardiac disorders and have beneficial synergistic action when combined with other antiarrhythmic drugs including amiodarone
- Amiodarone can be safely employed to control symptomatic tachyarrhythmias in post-infarction and heart failure patients
- Device therapy is superior to drug therapy in patients who have experienced a life-threatening episode of VT/VF
- Combination and hybrid therapy is, in many clinical settings, superior to monotherapy
- 'Upstream' therapy is gaining in importance in the management and prevention of arrhythmias
- To date, no antiarrhythmic drug (other than beta-blockers) has been shown to be of benefit in the primary prevention of sudden cardiac death. New trials enroling higher risk patients and employing novel agents (e.g. azimilide) are addressing this issue

Table 19.6
Overview of status of antiarrhythmic strategies.

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