Secondary prevention in patients with CHD

**ANTITHROMBOTICS**

10.1 What is the indication for aspirin use? 171
10.2 What are the contraindications to aspirin use? 171
10.3 What are its adverse effects? 172
10.4 What is the evidence base for its use? 172
10.5 What alternative antiplatelet agents are there? 172
10.6 How do thienopyridines work and when should they be used? 174
10.7 Is there a role for long term glycoprotein IIb/IIIa receptor antagonists? 174
10.8 Do oral anticoagulants have benefits? 175
10.9 Should warfarin be given long term? 175

**STATINS**

10.10 How do statins work? 177
10.11 What are the benefits of statins? 177
10.12 What are the indications for statin therapy? 178
10.13 What is the target cholesterol concentration with statin therapy? 178
10.14 What are the contraindications to statin therapy? 179
10.15 What are their adverse effects? 180
10.16 How soon after an acute coronary syndrome should statins be administered? 180
10.17 Are there differences between drugs in this class? 181
10.18 When should other (non-statin) lipid lowering agents be considered? 182

**β-BLOCKERS**

10.19 What are the benefits of β-blockers? 183
10.20 What are their adverse effects? 183
10.21 What is the evidence base for their use? 183
10.22 Are there differences between drugs in this class? 184
10.23 How long should β-blockers be given after myocardial infarction? 185
## ACE INHIBITORS

<table>
<thead>
<tr>
<th>Section</th>
<th>Question</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.24</td>
<td>How do ACE inhibitors work?</td>
<td>185</td>
</tr>
<tr>
<td>10.25</td>
<td>What are the benefits of ACE inhibitors?</td>
<td>186</td>
</tr>
<tr>
<td>10.26</td>
<td>Should ACE inhibitors only be used in patients with heart failure?</td>
<td>186</td>
</tr>
<tr>
<td>10.27</td>
<td>What are the contraindications to ACE inhibitors?</td>
<td>187</td>
</tr>
<tr>
<td>10.28</td>
<td>What are their adverse effects?</td>
<td>187</td>
</tr>
<tr>
<td>10.29</td>
<td>What is the evidence base for their use?</td>
<td>188</td>
</tr>
<tr>
<td>10.30</td>
<td>Are there differences between drugs in this class?</td>
<td>188</td>
</tr>
<tr>
<td>10.31</td>
<td>What alternative agents are there?</td>
<td>190</td>
</tr>
</tbody>
</table>

## MISCELLANEOUS

<table>
<thead>
<tr>
<th>Section</th>
<th>Question</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.32</td>
<td>Should hormone replacement therapy be given to postmenopausal women?</td>
<td>192</td>
</tr>
<tr>
<td>10.33</td>
<td>Should antioxidant vitamins be routinely given?</td>
<td>192</td>
</tr>
<tr>
<td>10.34</td>
<td>What is the evidence for fish oils?</td>
<td>193</td>
</tr>
<tr>
<td>10.35</td>
<td>What is the role of cardiac rehabilitation?</td>
<td>194</td>
</tr>
<tr>
<td>10.36</td>
<td>Who benefits most from cardiac rehabilitation?</td>
<td>195</td>
</tr>
</tbody>
</table>

## PATIENT QUESTIONS

<table>
<thead>
<tr>
<th>Section</th>
<th>Question</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.37</td>
<td>What is the best way of treating coronary heart disease?</td>
<td>196</td>
</tr>
<tr>
<td>10.38</td>
<td>Is diet important?</td>
<td>196</td>
</tr>
<tr>
<td>10.39</td>
<td>Is red wine good for the heart?</td>
<td>196</td>
</tr>
<tr>
<td>10.40</td>
<td>Is salt bad for the heart?</td>
<td>197</td>
</tr>
</tbody>
</table>
ANTITHROMBOTICS

10.1 What is the indication for aspirin use?

Aspirin is indicated for the secondary prevention of all forms of coronary heart disease (CHD). Patients with chronic stable angina, unstable angina and myocardial infarction all benefit from aspirin. These benefits are particularly seen with coronary revascularisation: percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery. Moreover, aspirin prevents cardiovascular events in patients with cerebrovascular and peripheral vascular disease.

10.2 What are the contraindications to aspirin use?

Aspirin therapy is contraindicated in patients with an aspirin allergy. A proper history should be obtained as allergic reactions are often over-reported and may not represent a true allergy. This is particularly important where a potentially life saving treatment, such as aspirin, is involved. In patients with a clear history of facial swelling and laryngeal oedema, aspirin should not be administered. In the absence of severe symptoms, and where doubt exists, re-challenging the patient may be appropriate.

There are several relative contraindications that reflect the adverse effects of aspirin. The decision to use aspirin depends upon the relative risks and benefits of therapy. The major hazards of aspirin treatment relate to an increased risk of bleeding complications or gastric ulceration. Patients at increased risk of bleeding include those with peptic ulcer disease, history of gastrointestinal haemorrhage, intracranial haemorrhage, concomitant oral anticoagulants and uncontrolled hypertension. Care should be taken when administering aspirin to people taking other non-steroidal anti-inflammatory drugs because this increases the risk of gastrointestinal problems and may lessen the benefit of aspirin.

In patients undergoing surgery, aspirin should be continued in the perioperative period as this will reduce perioperative cardiovascular complications and events. However, if the risks of bleeding are unacceptably high, aspirin should be withdrawn 5–7 days before surgery.

In occasional patients, aspirin can exacerbate asthma. Again, the risks and benefits should be considered but the vast majority of patients with asthma are able to tolerate aspirin well and should not be denied the preventative benefits of aspirin in the presence of concomitant vascular disease.

Where aspirin is contraindicated, clopidogrel is an appropriate alternative (see below).
10.3 What are its adverse effects?

As with all effective antiplatelet agents, there is a small but significant increased risk of bleeding associated with aspirin use. For secondary prevention in patients with CHD, these risks are invariably outweighed by the major benefits of avoiding cardiovascular events (see Q. 6.33).

There are theoretical risks of aspirin therapy in patients with asthma and bronchospasm. In a minority of patients, this can create major problems in the control of their respiratory disease. This can occur in patients with severe acute and recurrent exacerbations, mediated through the unwanted effects of aspirin on leukotrienes. Inhibition of potential bronchial relaxation can have adverse effects. However, the majority of patients with asthma, irrespective of disease severity, tolerate aspirin well without deterioration in bronchial reactivity.

10.4 What is the evidence base for its use?

There have been many randomised controlled trials of aspirin use in cardiovascular disease. This evidence base is substantial and the benefits incontrovertible in the context of CHD.

The Antiplatelet Trialists’ Collaboration performed the definitive meta-analysis of aspirin use, reporting a relative reduction in the future risk of cardiovascular events and a reduction in the incidence of non-fatal myocardial infarction (see Q. 6.34). These benefits were consistently seen across the broad spectrum of CHD, including patients with chronic stable angina, unstable angina and myocardial infarction, and aspirin therapy has been shown to have particular benefits in patients who have undergone coronary revascularisation – either PCI or CABG surgery.

10.5 What alternative antiplatelet agents are there?

Aspirin is a relatively weak antiplatelet agent and this has encouraged the development of more effective antiplatelet agents (Fig. 10.1). There are three main classes of antiplatelet agent in addition to aspirin: dipyridamole, thienopyridines and glycoprotein IIb/IIIa receptor antagonists (see Q. 6.35). The latter two are discussed below (see Qs 10.6 and 10.7).

Dipyridamole is both a vasodilator and antiplatelet agent. It acts through inhibition of platelet phosphodiesterase and thereby blocks cyclic adenosine monophosphate conversion to adenosine triphosphate. This leads to inhibition of platelet adhesion, aggregation and lengthening of shortened platelet survival time. It does not appear to prevent cardiovascular events in patients with CHD. There is some limited evidence from a single large trial, the European Stroke Prevention Study 2, that combination dipyridamole and aspirin therapy may have a role in cerebrovascular disease. In meta-analyses, dipyridamole plus aspirin reduced vascular events but not deaths,
Fig. 10.1 Mechanism of action of various antiplatelet agents. AA, arachidonic acid; ADP, adenosine diphosphate; GP, glycoprotein; NO, nitric oxide; TXA₂, thromboxane A₂ (Adapted from Rang et al.² with permission of Elsevier.)
largely due to the influence of the European Stroke Prevention Study 2 results.

The Antiplatelet Trialists’ Collaboration has clearly established that dipyridamole does not have any role in the primary or secondary prevention or treatment of CHD.

10.6 How do thienopyridines work and when should they be used?

There are two main agents in this class: ticlopidine and clopidogrel (see Q. 6.35). Ticlopidine is no longer widely used in clinical practice for long term therapy because it has a small (1–2%) but significant risk of inducing potentially fatal neutropenia and agranulocytosis. This bone marrow toxicity is not a feature of clopidogrel, an analogue of ticlopidine.

The current evidence concerning the use of clopidogrel is summarised in Question 6.36 and indications for its use are given in Box 10.1. Current guidelines recommend the use of combined clopidogrel and aspirin therapy in patients with unstable angina or non-ST segment elevation myocardial infarction for at least 9 months. The majority of the benefits are, however, seen in the first 3 months. For patients who have undergone intracoronary stent implantation, previous practice was to administer combination clopidogrel and aspirin therapy for 4 weeks. However, recent evidence from the CREDO trial ($n = 2116$) suggests that this may be too short and many clinicians are now recommending longer treatment (2–12 months) after coronary intervention, especially where drug eluting stents have been employed.

10.7 Is there a role for long term glycoprotein IIb/IIIa receptor antagonists?

The glycoprotein IIb/IIIa receptor is the final common pathway through which platelets aggregate (see Fig. 10.1). Whilst these agents will prevent platelet aggregation whatever the stimulus, they do not inhibit platelet activation and degranulation.

The different types of glycoprotein IIb/IIIa receptor antagonist are described in Question 6.35.

**BOX 10.1 Indications for the use of clopidogrel**

- Secondary prevention of coronary heart disease in patients where aspirin is contraindicated, poorly tolerated or associated with unacceptable side-effects
- Combination therapy with aspirin in patients with unstable angina or non-ST segment elevation myocardial infarction
- Combination therapy with aspirin in patients who have undergone PCI and stent implantation
Glycoprotein IIb/IIIa receptor antagonists do not appear to have a role in the long term prevention or treatment of patients with CHD. In the SYMPHONY trial \((n = 9233)\), sibrafiban (low and high dose) was compared to aspirin in patients with a recent acute coronary syndrome. There was no difference in cardiovascular event rates between the three groups although sibrafiban was associated with an ~1.5-fold increased risk of major bleeding.

In the second SYMPHONY trial \((n = 6671)\), patients with a recent acute coronary syndrome were randomised to aspirin alone, high dose sibrafiban alone or aspirin plus low dose sibrafiban for at least 12 months. The trial was terminated early because of the results of the first SYMPHONY trial. There was no difference in the primary endpoint of the trial for the three treatment groups. However, sibrafiban was again associated with an increased bleeding risk but only when used in combination with aspirin. Of major concern, high dose sibrafiban increased both mortality (odds ratio (OR) 1.83; 95% confidence intervals (CI), 1.17–2.88) and the rate of myocardial infarction (OR 1.32; 95% CI, 1.03–1.69) in comparison to aspirin alone. There was also a similar trend with low dose sibrafiban plus aspirin therapy.

In summary, glycoprotein IIb/IIIa receptor antagonists have no role in the secondary prevention of CHD in patients already receiving aspirin or clopidogrel therapy.

10.8 Do oral anticoagulants have benefits?

There have been several studies to assess the efficacy of anticoagulants in the secondary prevention of CHD. These have principally employed warfarin as either a fixed low dose regimen or dose adjusted to maintain therapeutic anticoagulation. A meta-analysis of over 20 000 patients with CHD has shown a clear benefit of oral anticoagulants in the secondary prevention of CHD\(^5\) (see Box 10.2).

10.9 Should warfarin be given long term?

As detailed above, there is convincing evidence that oral anticoagulation has significant secondary preventative benefits in patients with CHD even in the absence of atrial fibrillation. The widespread uptake of warfarin has been limited and unpopular because of the implications of therapy and monitoring as well as the major bleeding risk. The use of lower intensity anticoagulation regimens (INR <2.0) combined with aspirin is associated with loss of secondary preventative efficacy whilst maintaining the bleeding risk. Thus where there is concern about the bleeding risks, combination therapy should be avoided and isolated aspirin or clopidogrel considered.

The bleeding risks are largely driven by warfarin rather than aspirin and only patients with a low bleeding risk should be considered for warfarin therapy. Although warfarin plus aspirin is more effective than aspirin alone, it remains unclear whether it is better than warfarin alone. As with atrial
BOX 10.2 Data concerning the benefits of oral anticoagulation

- **Oral anticoagulation versus control**: In 13 trials (n = 8140), high intensity anticoagulation (INR >2.8) was compared to an inactive control. In these studies, oral anticoagulation produced a dramatic reduction in cardiovascular death, myocardial infarction or stroke from 30.3 to 20.3% (RRR 42%; 95% CI, 36–48%). However, this was associated with a marked increase in bleeding risk from 0.7 to 4.6% (odds ratio 4.5; 95% CI, 2.5–6.0). Lower intensities of anticoagulation (INR 2.0–3.0) have not been shown to provide significant preventative benefits but do lead to an increased risk of major bleeding.

- **Oral anticoagulation versus aspirin**: In six trials (n = 4155), oral anticoagulation had significant additional benefits in comparison to aspirin alone. The rate of death, myocardial infarction and stroke was 13.5% on oral anticoagulation and 16.3% on aspirin (RRR 21%; 95% CI, 6–33%). This was associated with a 2.1-fold increased risk of major bleeding.

- **Oral anticoagulation plus aspirin versus aspirin alone**: The combination of aspirin and oral anticoagulation also has additive benefits as demonstrated in seven trials totalling 12 333 patients. In comparison to aspirin alone, the rate of cardiovascular death, myocardial infarction and stroke was reduced from 17.6 to 15.9% (RRR 12%; 95% CI, 3–20%). Major bleeding events occurred in 3.0% compared with 1.7% respectively, a 1.74-fold increase.

- **Oral anticoagulation plus aspirin versus oral anticoagulation alone**: As with aspirin alone, oral anticoagulation plus aspirin appears to be better than oral anticoagulation alone. However, the data are limited and involve only three trials incorporating 3142 patients. While the RRR for cardiovascular death, myocardial infarction and stroke appears to be comparable (14%; 95% CI, 6% to +30%) this did not achieve statistical significance (p = 0.15). The major bleeding risks appeared to be very similar: 2.2% for combination therapy compared with 2.3% for oral anticoagulation alone.

- **Other oral agents**: The recent ESTEEM trial (n = 1883) examined the benefits of ximelagatran, a novel oral direct thrombin inhibitor, in patients with a myocardial infarction. Ximelagatran has the advantage that its pharmacodynamic effects are more predictable and, unlike warfarin, it does not require regular monitoring or dose adjustments. This trial also demonstrated a significant reduction from 16.3 to 12.7% (RRR 24%; 95% CI, 2–41%) in the risk of death, recurrent myocardial infarction or severe myocardial ischaemia. Major bleeding events were again increased from 0.9 to 1.8%, a 1.97-fold increase.

CI, confidence intervals; INR, international normalised ratio; RRR, relative risk reduction.
fibrillation, the benefits must be balanced with the major bleeding risks. For many patients, the latter is a major consideration. Warfarin, used alone or in combination with aspirin, may be considered in patients who are at very high cardiovascular risk or who have sustained recurrent cardiovascular events despite aspirin therapy.

Recently, direct oral thrombin inhibitors have been developed that have a more predictable therapeutic range and do not require monitoring of the prothrombin time. Ximelagatran is the first such inhibitor that is now in advanced phase III clinical trials. It is likely that ximelagatran will have very similar secondary preventative benefits in CHD to warfarin but this remains to be established.

**STATINS**

10.10 How do statins work?
Statins inhibit the enzyme hydroxy-3-methyl glutaryl coenzyme A (HMG CoA) reductase. This is the rate-limiting enzyme in the cholesterol synthetic pathway and converts HMG CoA to mevalonate. Inhibition of the HMG CoA reductase enzyme with statins causes marked reductions in cholesterol synthesis and reduces total and low density lipoprotein (LDL) cholesterol concentrations. Some agents also have modest beneficial effects on increasing high density lipoprotein (HDL) cholesterol concentrations and reducing triglyceride concentrations. The reduction in serum cholesterol concentrations produces marked beneficial clinical effects by reducing plaque progression and atherogenesis.

Recently, there has been interest in the cholesterol-independent effects of statins: their so-called ‘pleiotropic effects’. Several lines of evidence suggest that statins may directly affect other pathways involved in atherogenesis: these include improving endothelial function, decreasing vascular inflammation and enhancing plaque stability. There are also intriguing observations suggesting that statins may have very diverse effects such as the prevention of osteoporosis. The role and importance of these pleiotropic effects remain to be established.

10.11 What are the benefits of statins?
Statins potently inhibit the synthesis of cholesterol and reduce serum total and LDL cholesterol concentrations. This inhibits plaque growth and leads to plaque stabilisation. Several observational studies have demonstrated that statins reduce lipid-rich pools and thicken the fibrous cap of atherosclerotic plaques. This leads to plaque stabilisation and a consequent reduction in cardiovascular events, myocardial infarction and death.

Across the spectrum of atherosclerotic disease (coronary heart disease, cerebrovascular disease and peripheral vascular disease), patients benefit
from statin therapy. Long term statin therapy is associated with major reductions in the risk of non-fatal myocardial infarction, coronary death, stroke and coronary revascularisation.

10.12 What are the indications for statin therapy?
There have been several large scale, randomised controlled trials to address the issue of lipid lowering therapy in patients with CHD. The 4S trial \((n = 4444)\) was the first to demonstrate a significant improvement (relative risk reduction (RRR) 30%) in mortality with the use of simvastatin in patients with CHD and a serum cholesterol concentration greater than 5.5 mmol/L. These mortality benefits have subsequently been shown not only with simvastatin but also with pravastatin. Primary and secondary preventative benefits have also been demonstrated with atorvastatin, fluvastatin and lovastatin.

At present, the goal of therapy would appear to be suppression of the serum total cholesterol concentration to at least below 5.0 mmol/L. The CARE \((n = 4159)\), LIPID \((n = 9014)\), MIRACL \((n = 3086)\) and Heart Protection \((n = 20 536)\) studies have additionally suggested that patients with average cholesterol concentrations or lower should also be considered for lipid lowering therapy as it is associated with similar relative risk reductions in future adverse cardiac events. However, the target cholesterol seems unclear (see Q. 10.13).

10.13 What is the target cholesterol concentration with statin therapy?
At present, there are no clear evidence-based data to address this question. Historically, the randomised controlled trials arbitrarily chose 5.0 mmol/L as the target of total cholesterol concentration. However, the studies do not permit us to determine if 5.5 mmol/L is adequate or if 4.5 and lower will achieve further benefits. At present, the Joint British Cardiac, Diabetic, Hypertension and Hyperlipidaemia Societies currently recommend that all patients with CHD should receive statin therapy with the target of reducing their serum total cholesterol below 5.0 mmol/L. It is likely that this threshold concentration will be reduced further. However, there are strong arguments to lower the cholesterol whatever the absolute serum cholesterol concentration. The data from the CARE, HPS, MIRACL and ASCOT-LLA trials suggest it is the overall absolute risk that is important rather than the cholesterol concentration per se. If a patient is at high risk, they will benefit from cholesterol reduction irrespective of their cholesterol concentration. For example, in the Heart Protection Study, patients with a total cholesterol concentration less than 5.0 mmol/L had a 5-year event rate of
22.1% that was reduced to 16.9% by simvastatin 40 mg daily. Thus a patient with a recent myocardial infarction, diabetes mellitus and peripheral vascular disease will merit statin therapy even if their total cholesterol concentration is 3.6 mmol/L.

Some authorities have argued that the secondary preventative benefits of statins are independent of the serum cholesterol reductions and it is the pleiotropic effects of statins that account for their clinical utility. This, however, seems unlikely. There are several ongoing trials that are assessing whether more intensive lipid lowering with low and high dose or potency statins will lead to improved clinical outcomes. These trials will help us to guide the approach to cholesterol reduction in patients with CHD. A recent meta-analysis incorporating ~28 000 patients has suggested that greater reductions in serum LDL cholesterol concentrations are associated with more marked secondary preventative benefits.

There are some data from a randomised controlled trial that more intensive lipid lowering therapy will have additional benefits. Patients who have undergone saphenous vein bypass grafting appear to gain more benefit from intensive reductions in serum LDL cholesterol concentrations. In the Post Coronary Artery Bypass Graft trial ($n = 1351$), progression of atherosclerosis or vascular occlusion was reduced in patients treated to a serum LDL cholesterol concentration of <2.6 mmol/L compared to those treated to ~3.5 mmol/L. This was translated into reductions of clinical events including recurrent revascularisation.

Recently the PROVE-IT trial ($n = 4162$) demonstrated that more intensive lipid-lowering therapy with atorvastatin 80 mg was superior to more modest cholesterol reduction with pravastatin 40 mg daily. This would appear to suggest that intensive cholesterol reduction is more beneficial, especially where LDL cholesterol is ≥3.2 mmol/L.

10.14 What are the contraindications to statin therapy?

Statins are generally very well tolerated with few adverse effects. The main contraindications of statins relate to their potential adverse effects on the liver and skeletal muscle that may be increased by other concomitant medications such as fibrates. Other contraindications include women of child-bearing potential, pregnancy, breast feeding and porphyria.

Statin therapy can lead to elevations in liver enzymes, particularly transaminases. Patients with active liver disease should, therefore, not receive statin therapy. Transient rises in the transaminases are common early after initiation of statin therapy but rarely (<1%) rise above three times the upper limit of normal. It is recommended that liver function tests are documented before initiating treatment and monitored for at least the first few months of therapy.
10.15 What are their adverse effects?

Statins can occasionally cause myopathy. This may be manifest as generalised myalgia with or without elevation in skeletal muscle enzymes, such as creatine kinase. Many patients complain of tiredness and myalgia on routine inquiry. Statins should not be discontinued unless there is a clear causal association between drug and symptoms. Trial withdrawal of therapy and re-challenging with the statin may be appropriate. In the Heart Protection Study, myalgia was reported by 32.9% of patients allocated simvastatin and 33.2% of patients allocated placebo.

Myositis and rhabdomyolysis are very rare but important adverse effects. Elevation of the creatine kinase 10 times the upper limit of normal occurs in 0.1% of patients and rhabdomyolysis in ~0.05%. In the randomised controlled trials, these rates are very similar to those seen in patients taking placebo (0.06% and 0.03% respectively). Although the adverse effects of statins are rapidly reversible on discontinuation of therapy, statin-induced rhabdomyolysis has ~10% mortality. Patients with a known prior or current myopathy should not receive statin therapy.

10.16 How soon after an acute coronary syndrome should statins be administered?

It should be recognised that patients presenting with an acute coronary syndrome will experience a fall in their serum cholesterol concentrations as a consequence of the acute illness which can last for up to 3 months. It is, therefore, preferable to assess the serum lipid profile within 24 hours of symptom onset. Patients should not have been judged to reach their target cholesterol until after at least 12 weeks of convalescence.

The original statin trials (4S, CARE, LIPID) excluded patients who had an acute coronary syndrome within 4–6 months. This exclusion was imposed because of the uncertain safety profile of this class of drug. Following the publication of the landmark trials, the question of whether it was safe or indeed beneficial to introduce statin therapy early after an acute coronary syndrome was resolved by observational studies which suggested that early statin use was associated with major reductions in subsequent and early recurrent cardiovascular events.

The MIRACL trial (n = 3086) recruited patients within 4 days of an acute coronary syndrome and randomised them to atorvastatin 80 mg daily or placebo for 16 weeks. Patients with significant hypercholesterolaemia (>7.0 mmol/L) were excluded but there was no lower limit of cholesterol concentration for inclusion in the trial. Although this was a very short term trial (16 weeks compared to the 5 years of previous trials), there was a significant reduction in the primary endpoint from 17.4 to 14.8% (p = 0.048). This benefit was largely driven by a reduction in recurrent
severe ischaemia requiring re-hospitalisation (8.4 to 6.2%; RRR 24%, p = 0.02). This result is, in some ways, remarkable given the very brief period of treatment. This indicates that not only is statin therapy safe immediately after an acute coronary syndrome but it is also probably beneficial if given early. This presumably reflects the advantageous remodelling effects of lipid lowering therapy following acute plaque rupture.

Statins should be administered early after a patient presents with an acute coronary syndrome.

10.17 Are there differences between drugs in this class?

There are several important differences between the types of statin therapy.

**Efficacy**

The reduction in serum cholesterol concentrations varies markedly between the types of statin. Comparative trials have indicated that significant differences exist (*Table 10.1*). Pravastatin and fluvastatin appear to produce modest reductions in serum cholesterol concentrations, simvastatin and lovastatin cause moderate reductions whereas atorvastatin and rosuvastatin lead to the greatest reductions in cholesterol concentrations.

**Evidence Base**

The statins that have been assessed in major randomised controlled trials of primary and secondary prevention are:

- Pravastatin – WOSCOPS, CARE and LIPID trials
- Simvastatin – 4S and HPS trials
- Atorvastatin – ASCOT-LLA and MIRACL trials
- Fluvastatin – LIPS and FLARE trials
- Lovastatin – AFCAPs/TEXCAPs trial.

**Table 10.1 Reduction in baseline serum LDL cholesterol concentrations**

<table>
<thead>
<tr>
<th>Statin</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin</td>
<td>15%</td>
<td>21%</td>
<td>27%</td>
<td>33%</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>20%</td>
<td>24%</td>
<td>29%</td>
<td>33%</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>21%</td>
<td>29%</td>
<td>37%</td>
<td>45%</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>27%</td>
<td>32%</td>
<td>37%</td>
<td>42%</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>37%</td>
<td>43%</td>
<td>49%</td>
<td>55%</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>43%</td>
<td>48%</td>
<td>53%</td>
<td>58%*</td>
</tr>
</tbody>
</table>

*Rosuvastatin 80 mg is currently unlicensed because of safety concerns.
SAFETY

The incidence of serious adverse effects is not the same for all statins. This, in part, reflects how the different statins are metabolised.

Simvastatin can interact with drugs that inhibit the cytochrome P<sub>450</sub> 3A4 enzyme and these include phenazone, propranolol, digoxin and warfarin and other coumarin derivatives. To avoid potential interactions, simvastatin is often given late in the evening. Cerivastatin has a similar and more marked interaction with the cytochrome P450 3A4 enzyme. This interaction led to a much higher incidence of statin-associated rhabdomyolysis and resulted in the recent withdrawal of cerivastatin from the market. Cerivastatin was responsible for more than half of all the reported cases of rhabdomyolysis.

There are now extensive safety data on most statins and there is clear evidence that the current evidence-based statins are safe and have a good side-effect profile.

10.18 When should other (non-statin) lipid lowering agents be considered?

There are many non-statin agents that lower cholesterol concentrations: fibrates, resins, niacin, ezetimibe. However, although these drugs lower serum lipid concentrations, they have not been clearly shown to reduce mortality in randomised controlled trials. These agents are usually reserved for patients who have contraindications to statin therapy or are used as adjunctive therapy in patients who have resistant hypercholesterolaemia despite statin therapy. It should be remembered that the adverse effects of statins are potentiated by other lipid lowering therapies.

- Fibrates have a direct action on the liver to reduce triglyceride concentrations and, to a variable extent, LDL cholesterol concentrations. They may also increase HDL cholesterol concentrations and may be particularly useful in those patients with low HDL cholesterol concentrations. In the VA-HIT trial (n = 2531), gemfibrozil 1.2 g daily had modest benefits in patients with CHD and a normal LDL cholesterol concentration (≤3.7 mmol/L) but a reduced HDL cholesterol concentration (≤1.0 mmol/L). Its use was associated with a 22% relative risk reduction (95% CI, 7–35%) in major adverse cardiac events but no effect on overall mortality.

- Resins, such as colestyramine and colestipol, bind bile acids and prevent their intestinal reabsorption. This promotes bile acid synthesis and reduces LDL cholesterol concentrations. This may be used in association with other therapies to reduce serum cholesterol concentrations but their use is associated with extensive gastrointestinal side-effects and may adversely increase triglyceride concentrations.
Niacin and nicotinic acid derivatives are limited by the marked side-effects which include vasodilatation, flushing, rashes and gastrointestinal upset. These agents produce very modest effects on lipid levels.

Ezetimibe is a new class of lipid lowering therapy that acts through reductions in intestinal cholesterol absorption. It is currently indicated as adjunctive therapy in patients with resistant hypercholesterolaemia.

---

**β-BLOCKERS**

10.19 What are the benefits of β-blockers?

β-blockers are antagonists at β-adrenoceptors, and thus produce negative chronotropism and negative inotropism in the heart. The attenuation of the heart rate response to exercise and stress reduces the myocardial oxygen demand and severity of ischaemia. It also prolongs diastole, a major determinant of myocardial perfusion time. Randomised controlled trials have demonstrated that β-blocker therapy is efficacious in reducing symptoms of angina, episodes of ischaemia and improving exercise capacity.

The indications for β-blockers are expanding. There is clear evidence that β-blockade has major morbidity and mortality benefits in patients with myocardial infarction and chronic heart failure, reducing the risk of recurrent myocardial infarction and death.

10.20 What are their adverse effects?

True side-effects from β-blocker therapy are uncommon (<10%) but do include symptoms, such as fatigue and lethargy, which are commonly encountered on routine enquiry. A causative association should, therefore, be established before permanently discontinuing β-blocker therapy. Because of β-adrenergic receptor upregulation in the presence of β-blockade, patients should not be withdrawn from therapy rapidly. This can cause an acute withdrawal syndrome and there is a suggestion that this may even precipitate acute myocardial infarction.

10.21 What is the evidence base for their use?

Meta-analyses (n = 54 234) have demonstrated that β-blockers have a major benefit in reducing the risk of death by 23% in patients after an acute myocardial infarction. These benefits are demonstrable for at least the first 2 years and are probably sustained beyond this. Hypertension and case-control studies have also shown that patients maintained on β-blockers are less likely to have a major adverse cardiac event and have a reduced mortality if they subsequently suffer a myocardial infarction. For these
reasons, β-blockers should be considered in patients with CHD and hypertension.

Hypertension and angina trials indicate that β-blockers are better tolerated and have fewer side-effects than other commonly prescribed agents, such as calcium channel antagonists. Concerns that β-blocker therapy is associated with reduced peripheral perfusion in patients with peripheral vascular disease are unfounded. β-blockers may have significant secondary preventative benefits in these patients as suggested by the marked reductions in perioperative mortality and myocardial infarction when undergoing major vascular surgery.

Because of the common risk factor of smoking, many patients with angina have chronic obstructive pulmonary disease and are denied β-blocker therapy due to the concern of provoking bronchospasm. Observational data demonstrate that patients with obstructive pulmonary disease derive similar mortality benefits (RRR 40%) following myocardial infarction with β-blocker therapy. Therefore, such patients should be given a trial β-blockade since the majority tolerate therapy well. If there is genuine concern of clinically significant reversible bronchospasm, formal spirometry in the presence and absence of a β₂ agonist, such as nebulised salbutamol 5 mg, should be performed.

Patients with ischaemic heart disease and coexisting heart failure are particularly at risk and should also be given β-blocker therapy as the agent of choice. There have been several large scale, randomised controlled trials that have demonstrated major mortality and morbidity benefits in patients with mild to severe heart failure maintained on β-blocker therapy. Metoprolol (MERIT-HF trial, \( n = 3991 \)), carvedilol (programme of trials, \( n = 1094 \)) and bisoprolol (CIBIS II, \( n = 2647 \)) have all been shown to reduce mortality by at least 34% in patients with heart failure maintained on ACE inhibitor therapy. Despite theoretical and prejudicial concerns, β-blockers improve both morbidity and mortality in this important group of patients. There is, however, concern with regard to the initiation of therapy in patients with heart failure because of the potential to precipitate acute decompensation. It is currently recommended that β-blockade is initiated slowly with a cautious uptitration over a 6–8 week period. Several initiatives are being explored in order to facilitate this uptitration phase including heart failure liaison nurses and starter packs.

10.22 Are there differences between drugs in this class?

There is no evidence to support the suggestion that one type of β-blocker is superior to another. The so-called highly selective β₁ blockers (e.g. celiprolol or bisoprolol), or those with combined vasodilating and antioxidant properties (e.g. carvedilol), have no proven benefits above conventional β-blockers (e.g. atenolol or metoprolol). However, the secondary preventative benefits
of β-blockers may be lost where agents have intrinsic sympathomimetic action and the use of such agents should, therefore, be avoided.

The COMET trial (\(n = 3029\))\(^{11}\) did compare two β-blockers, carvedilol and metoprolol, in the treatment of chronic heart failure. There was a modest favourable effect of carvedilol in comparison to metoprolol. However, this trial used an inappropriately low dose of metoprolol and it cannot be viewed as demonstrating superiority of one β-blocker over another.

10.23 How long should β-blockers be given after myocardial infarction?

This is a contentious area. The trials of β-blockade in patients who had sustained an acute myocardial infarction were conducted before the advent of large scale, randomised controlled trials. Many trials had a limited follow-up and did not assess the long term benefits. The evidence is, therefore, limited to 2 years post myocardial infarction and there is general agreement that β-blockade should be given to all patients for at least the first 2 years after myocardial infarction.

After 2 years, there are differing views as to the merits of continuing β-blockade. Meta-analyses indicate that the benefits are indeed sustained after 2 years and there is no suggestion of loss of benefit over time. Clearly, where there is evidence of significant left ventricular dysfunction, trial evidence would support the use of indefinite β-blocker therapy. However, where there is preserved left ventricular function, continuation of β-blockade beyond 2 years is less clear. It would seem sensible to continue therapy where there is an additional indication, such as hypertension or angina pectoris, or where it is well tolerated. Withdrawal of β-blockade can be associated with major adverse effects.

ACE INHIBITORS

10.24 How do ACE inhibitors work?

Angiotensin converting enzyme (ACE) is present on the endothelial cell surface and converts angiotensin I to angiotensin II. Angiotensin II causes marked arterial vasoconstriction, as well as salt and water retention, leading to an increase in vascular resistance, blood volume and arterial pressure. However, ACE was also identified as an enzyme that metabolises bradykinin. Indeed, it has a higher substrate affinity for bradykinin than angiotensin I. The benefits of ACE inhibition are likely to relate to both the inhibition of the renin–angiotensin–aldosterone system as well as the potentiation of bradykinin action.

Inhibition of ACE has a weak vasodilator and vasodepressor effect. This is particularly marked where there is activation of the renin–angiotensin–
aldosterone system, such as with concomitant potent diuretic therapy. This reduces cardiac afterload and inhibits salt and water retention. There are also potentially beneficial effects on heart rate variability and left ventricular remodelling, particularly after acute myocardial infarction. ACE inhibitors also have beneficial effects on vascular function that improve endothelial dysfunction, enhance endogenous fibrinolysis and reduce vascular inflammation.

10.25 What are the benefits of ACE inhibitors?

All patients with CHD should be considered for maintenance ACE inhibitor therapy because of the major secondary preventative benefits. ACE inhibition is associated with a significant reduction in death, myocardial infarction, stroke, renal failure, diabetes mellitus and hypertension. In particular, ACE inhibition appears to have an anti-ischaemic effect and consistently reduces the risk of myocardial infarction by ~20%.

ACE inhibition produces symptomatic benefits in patients with heart failure and is associated with improvements in New York Heart Association (NYHA) class and exercise capacity. In patients with preserved left ventricular function, ACE inhibition does not have any specific symptomatic benefits but does improve prognosis in patients with a wide range of vascular disease and associated risk factors.

10.26 Should ACE inhibitors only be used in patients with heart failure?

The major morbidity and mortality benefits of ACE inhibitor therapy were first demonstrated in patients who were at the greatest risk – those with overt heart failure. These benefits are, at least in part, likely to reflect an anti-ischaemic action of ACE inhibition, particularly given the reduction in re-infarction rates seen in all the major randomised controlled trials.

The HOPE study ($n = 9297$) was a large scale, randomised controlled trial of ramipril 10 mg daily in patients with vascular disease (55% having chronic stable angina) without heart failure. During the 4.5 years of follow-up, ramipril was associated with reductions in all-cause mortality, myocardial infarction and stroke. Moreover, these beneficial effects appeared to be independent of the associated reductions in blood pressure, and are particularly marked in patients with diabetes mellitus. The EUROPA trial ($n = 1218$) was a large scale, randomised controlled trial of perindopril 8 mg daily in relatively low risk patients with coronary artery disease. After 4 years of follow-up, there was a 20% reduction in the risk of cardiovascular death, myocardial infarction or cardiac arrest.

There is now clear and consistent evidence that ACE inhibition should be given to all patients with coronary artery disease irrespective of left ventricular function. This is associated with a significant reduction in the
risk of myocardial infarction: consistent 20–22% relative risk reduction in all trials. The beneficial effects on mortality appear to depend upon the overall cardiovascular risk of the patient: greatest in those with severe left ventricular dysfunction and least in those at low risk with preserved left ventricular dysfunction.

10.27 What are the contraindications to ACE inhibitors?
Angiotensin converting enzyme inhibition should be avoided in patients with critical renovascular disease. Severe renal artery stenosis generates marked elevations in serum renin and angiotensin II concentrations that attempt to sustain renal perfusion pressure. Inhibition of ACE may, therefore, cause marked renal hypoperfusion and renal failure. Unless treatment is protracted or perfusion critical, ACE inhibitor induced renal dysfunction is usually reversible after cessation of therapy.

Occasionally, ACE inhibition may lead to acute precipitous hypotension that can cause dizziness, light-headedness and syncope. This is, however, unusual and can be avoided by longer acting ACE inhibitors, cautious up titration and nocturnal dosing.

Because of the occasional precipitous hypotension, it is normal practice to avoid ACE inhibitors in patients with severe aortic stenosis. There is no evidence base for this approach and some have argued that ACE inhibition may be of benefit, particularly in those patients with heart failure secondary to severe aortic stenosis. It would seem pertinent to avoid short acting ACE inhibitors that are associated with more marked acute changes in blood pressure, such as captopril. However, cautious introduction of ACE inhibition may have benefits in patients with heart failure due to aortic stenosis. For those patients with critical aortic stenosis unknowingly maintained on long term ACE inhibitor therapy, treatment should be continued unless there are major contraindications or severe side-effects.

ACE inhibition is contraindicated in women of child-bearing potential and in pregnancy. Depending upon the preparation, it should also be avoided in mothers who are breast feeding.

10.28 What are their adverse effects?
There are several adverse effects of ACE inhibitor therapy. Renal dysfunction is common and, following commencement of therapy, initial monitoring of renal function is mandatory because occasionally renal failure may rapidly ensue. This is usually reversed on discontinuation of therapy.

Hyperkalaemia may occur, especially when co-administered with potassium-sparing diuretics such as spironolactone or triamterene. Rarely, this may lead to serious hyperkalaemia in the presence or absence of renal failure.
Symptomatic hypotension, dizziness and light-headedness are occasional features of ACE inhibition. This usually occurs when initiated in patients with prior relative hypotension or already receiving potent diuretic therapy.

A dry, tickly, non-productive cough is also a characteristic side-effect of ACE inhibition. Its prevalence is probably over-reported. Cough is a common symptom and a clear causative relationship should be established. Many patients with an upper respiratory tract infection have their ACE inhibitor therapy discontinued unnecessarily. However, it can be an intolerable and irritating side-effect for a substantial number of patients; prevalence is 5–10%.

ACE inhibition may be associated with the development of angio-oedema. This is fortunately a very rare occurrence but can be life threatening if orolaryngeal oedema occurs. The incidence of this side-effect appears to be increased in certain ethnic groups (e.g. African-Americans) and the concomitant use of neutral endopeptidase inhibitors.

### 10.29 What is the evidence base for their use?

There is a large evidence base for ACE inhibition in patients with CHD. The mortality benefits appear to relate to the overall risk of the population. Early trials were performed in high risk patients with heart failure due to left ventricular systolic dysfunction: mortality at 4 years of ~30%. A meta-analysis of the major randomised controlled trials \( n = 12,763 \) demonstrated that ACE inhibition reduced total mortality by 20%.\(^{14}\) In the HOPE trial \( n = 9,297 \),\(^{12}\) patients with moderate risk had a mortality rate of 12% over 4 years and ramipril reduced total mortality by 16%. The recent EUROPA trial \( n = 12,218 \)\(^{13}\) (Fig. 10.2) had a similar risk population with a 4-year mortality rate of 17%. Perindopril reduced total mortality by 14%. However, irrespective of the overall risk, ACE inhibition appears to have a remarkably consistent benefit in reducing the future risk of myocardial infarction: 20–22% relative risk reduction in the rate of myocardial infarction.

Although proportional to overall cardiovascular risk, there is a large evidence base that supports the use of ACE inhibition in all patients with CHD.

### 10.30 Are there differences between drugs in this class?

There are several important differences between the various ACE inhibitor drugs. The main differences relate to the pharmacokinetics, tissue penetration and evidence base.

**PHARMACOKINETICS**

Captopril was the first ACE inhibitor to be employed in widespread clinical use. It also has the shortest plasma half-life and is administered two or three
times daily. This has the potential to have marked peak and trough effects with large swings in blood pressure. Acute captopril dosing is, therefore, more likely to induce symptomatic hypotension and dizziness.

Some agents rely upon a longer acting active metabolite, such as enalapril and enalaprilat, to cause less marked swings in blood pressure. However, newer agents, such as lisinopril, ramipril and perindopril, have a long half-life and produce more gradual but sustained reductions in blood pressure. The latter may be better tolerated and easier to administer in the community.

**TISSUE PENETRATION**

Some ACE inhibitor agents penetrate tissues less easily. Much has been made about the better and more complete tissue penetration of some ACE inhibitors, such as quinapril, lisinopril and perindopril. Tissue ACE inhibition may be more important for the beneficial effects on factors such as left ventricular hypertrophy and remodelling. Given that ACE is
predominantly expressed on the endothelial cell surface, tissue penetration is perhaps overemphasised in terms of the vascular actions of these agents.

**EVIDENCE BASE**

The early evidence base for ACE inhibitor therapy has predominantly been demonstrated with captopril and enalapril in patients with heart failure. Subsequent trials were performed in patients who had sustained an acute myocardial infarction with or without heart failure. The evidence base was then extended to include lisinopril, ramipril and trandolapril. Recent trials have now included patients without prior infarction or heart failure and included ramipril and perindopril.

10.31 What alternative agents are there?

ACE inhibitor drugs have significant side-effects and are not well tolerated by up to a third of patients. There are alternative therapies that can be used as second line therapy. Angiotensin II type 1 receptor antagonists, so-called angiotensin receptor blockers (ARBs), have been developed as an alternative and potentially more effective approach to inhibiting the renin–angiotensin system.

The early ELITE study \((n = 722)^{15}\) suggested that the ARB, losartan, had more marked beneficial secondary preventative benefits than the ACE inhibitor, captopril. However, the ELITE II study \((n = 3152)^{16}\) was unable to confirm these initial tentative findings and losartan was not found to be superior to captopril (Fig. 10.3). Indeed, the ELITE II and OPTIMAAL\(^{17}\) trials suggested a potential superiority of captopril over losartan. In all of these trials, losartan was better tolerated with fewer side-effects than captopril.

The Val-HeFT (valsartan, \(n = 5010\)) and CHARM-Alternative (candesartan, \(n = 2028\)) trials have recently assessed the benefits of ARBs in patients with heart failure who are unable to tolerate ACE inhibitor therapy. In these patients, ARBs have significant morbidity and mortality benefits although the magnitude of these benefits appears to be more modest than those associated with ACE inhibitors.

Patients may not be able to tolerate ACE inhibitor therapy not only because of troublesome side-effects but also because of renal dysfunction. While ARBs are appropriate for the former, the ELITE study demonstrated that ARBs cause similar degrees of renal dysfunction as ACE inhibitors. Thus where patients with heart failure are intolerant of ACE inhibitors due to renal dysfunction, ARBs should be avoided and the combination of hydralazine and nitrates considered since this was associated with very modest benefits in the early V-HeFT I \((n = 642)\) trial.

There are currently no randomised controlled trials to assess specifically the role of ARBs in patients with CHD and preserved left ventricular dysfunction. The CHARM-Preserved trial \((n = 3023)^{18}\) randomised patients
Fig. 10.3 Comparison of losartan and captopril. (From Pitt et al. with permission.)
with symptomatic heart failure and preserved left ventricular function (ejection fraction >40%) to candesartan or placebo. Over half of the patients had CHD as the underlying aetiology of heart failure. Overall, mortality was identical in both groups although candesartan did reduce the frequency of recurrent hospitalisations for heart failure by 18%.

Angiotensin receptor blockers are currently only indicated in patients with CHD if they also have heart failure.

**MISCELLANEOUS**

10.32 Should hormone replacement therapy be given to postmenopausal women?

Large observational studies have suggested that hormone replacement therapy (HRT), and in particular oestrogen, has a cardioprotective effect in women. However, there are many confounding factors in these observational studies such as the influence of socioeconomic class and motivation in women taking HRT. Moreover, pooled data from ongoing trials have so far failed to demonstrate a significant cardioprotective effect of HRT. The first randomised controlled trial of HRT, the HERS trial (n = 2763), failed to demonstrate a benefit with 5 years of HRT in postmenopausal women with CHD. Protagonists have suggested that the HERS trial may indicate an initial adverse effect of HRT which could be offset by protection against future cardiac events with long term (>3 years) sustained therapy. However, the HART trial (n = 226) failed to demonstrate a significant effect of HRT on the progression of atherosclerosis on coronary angiography over a 3.3 year follow-up. Finally, the Women’s Health Initiative trial (n = 16 608) failed to demonstrate any benefit of combined HRT in the primary prevention of CHD over 5.2 years of follow-up. Indeed, there was again a suggestion of an increased risk in the first year after commencing HRT.

Hormone replacement therapy has no role in the primary or secondary prevention of CHD and its routine use cannot be advocated. In patients who develop CHD while taking HRT, there is no evidence to suggest a benefit of discontinuing therapy. In women wishing to take HRT because, for example, they may have troublesome symptoms of the menopause, HRT should be administered following clinical assessment and treatment of risk factors for CHD.

10.33 Should antioxidant vitamins be routinely given?

There has been a major interest in the role of oxidation in the pathogenesis of atherosclerosis: specifically, the role of oxidised LDLs in the formation of foam cells and atherosclerotic plaques. Moreover, there has been a large body of promising preclinical data to suggest that supplementation of the
diet with antioxidants can markedly inhibit atherogenesis.

Clinical observational cohort studies have also indicated major reductions in mortality and cardiovascular events in people taking antioxidant vitamins. These findings have formed the rationale for major randomised controlled trials of antioxidant vitamins in the primary and secondary prevention of CHD. With the exception of the CHAOS trial, these trials have failed to demonstrate a significant benefit of antioxidant vitamins. The aptly named CHAOS trial changed the dose of vitamin E during the conduct of the trial and the benefits were inconsistent, appearing to reduce only the incidence of non-fatal myocardial infarction.

A recent meta-analysis assessed the effects of vitamin E and \( \beta \)-carotene on long term cardiovascular morbidity and mortality. Data from seven trials of vitamin E incorporating 81,788 patients clearly demonstrated no effect of vitamin E supplementation on the separate endpoints of all-cause mortality, cardiovascular death, stroke or non-fatal myocardial infarction. These findings are consistent for both primary and secondary prevention of CHD.

There were eight major trials that assessed the effects of \( \beta \)-carotene and provided a total sample population of 138,113 patients. Meta-analysis identified no benefit of \( \beta \)-carotene therapy and, of concern, there was a small increased risk of all-cause (OR 1.07; 95% CI, 1.02–1.11) and cardiovascular (OR 1.1; 95% CI, 1.03–1.17) mortality.

Across a broad dose range, there is no consistent evidence to indicate a role of antioxidant vitamins in the secondary prevention of CHD. Indeed, in the case of \( \beta \)-carotene, there may be a small but significant adverse effect.

10.34 What is the evidence for fish oils?

There is increasing evidence to support the role of polyunsaturated fatty (omega-3) acids (docosahexaenoic acid, DHA, and eicosapentaenoic acid, EPA) or fish oils in both the primary and secondary prevention of ischaemic heart disease.

Following the observation that Greenland Eskimos and Japanese fishermen have a low death rate from cardiovascular disease, it was suggested that this could be related to their high dietary intake of fish. In the Seven Countries Study, vegetable foods, alcohol and fish consumption were inversely correlated with CHD mortality. Subsequent observational studies such as the Chicago Western Electric Study, the Zutphen Study and the usual care group in the Multiple Risk Factor Intervention Trial reported an inverse relationship between the daily dietary consumption of oily fish and the death rate from CHD in men. More recently an inverse relationship between fish consumption and omega-3 fatty acid intake and the risk of CHD, and in particular the risk of fatal CHD events, has been reported in women. Not all studies have demonstrated this inverse relationship although some benefit was observed on cardiovascular outcomes, even in
individuals with a low habitual intake of oily fish, and this benefit appears to be independent of other risk factors.

In the Physicians’ Health Study, the consumption of one or more portions of fish at least once a week was associated with a 52% reduction in the risk of sudden cardiac death, but no relationship was seen between fish consumption and the risk of a first myocardial infarction. This beneficial effect seems to be specific to oily fish since in the Seven Countries Study oily fish consumption of around 15 g/day was associated with a 34% reduction in the risk of ischaemic heart disease death, but there was no association with total or lean fish consumption. In the Honolulu Heart Study, oily fish appeared to offer particular protection to smokers from CHD.

Oily fish have been shown to reduce deaths from ischaemic heart disease in patients following acute myocardial infarction. In the diet and re-infarction (DART) study, the advice to eat at least two portions of oily fish each week was associated with a significant reduction in mortality. Furthermore, the GISSI-Prevenzione investigators demonstrated that a daily capsule containing 1 g of DHA/EPA reduced all-cause mortality and improved cardiovascular outcomes at 42 months. The dose of DHA/EPA was equivalent to fish five times a week. However, it should be recognised that this was not a proper double-blind, randomised controlled trial as there was no placebo therapy and this may have influenced the results.

10.35 What is the role of cardiac rehabilitation?

While cardiac rehabilitation began as an exercise based activity designed to combat the loss of cardiovascular fitness associated with prolonged bed-rest after myocardial infarction, the modern approach to rehabilitation recognises that in addition to the physical element there are psychological and social aspects to the rehabilitation process.

Modern cardiac rehabilitation should be about involving the patient in a process of ‘self-management’ of a chronic disease process in the same way as one would a diabetic. The aims of that process of rehabilitation are two-fold: first, to modify the disease process (secondary prevention), and second, to assist the patient to return to a ‘normal’ role in society. It is, therefore, a process of behavioural modification that should encourage adaptive behaviours in the patient which will assist those aims.

Central to the process of rehabilitation are pathology, impairment, disability and handicap (Box 10.3). Much of our management in cardiology is targeted at the levels of pathology and impairment. We prescribe drugs or undertake interventions to modify impairment that we believe to be responsible for the patient’s disabilities. We judge our success mainly by the modification of pathology or alleviation of impairment. Given the causal relationship between pathology or impairment, and disability or handicap, we expect that the
latter will improve. However, this correlation is relatively low: for example, the patient with minimal coronary disease who complains of intractable angina preventing even light exercise or the patient with an ejection fraction of 15% who denies breathlessness on exertion. Some of the variance may be explained by factors within the organ or the individual (e.g. collateralisation, vasospasm or tolerance to raised end diastolic pressure) but more often such disparities are due to other factors, such as the psychological state of the patient, their level of fitness or the demands which society makes on them. This is perhaps the strongest argument for an approach that, while recognising the importance of pathology and impairment, is targeted more directly at disability and handicap. A holistic approach to the patient requires consideration of all four elements – the integration of rehabilitation with medical and surgical management as described in the definition earlier.

Ask yourself whether your patient would be symptomatically better if he were fitter, whether he would be less distressed if he had a clearer understanding of his condition, whether managing his anxiety would improve his quality of life, or whether changing his behaviour might alter the natural history of his disease. If the answer to any of these is ‘yes’ then rehabilitation in some form should play a part in the management of his condition.

10.36 Who benefits most from cardiac rehabilitation?

Patients with new onset or resistant angina, recent myocardial infarction or recent coronary revascularisation benefit most from cardiac rehabilitation programmes.

In comparison to a sedentary lifestyle, regular physical activity is associated with approximately half the risk of future cardiac events. The benefits of regular exercise appear to relate, in part, to the associated

---

**BOX 10.3 Rehabilitation**

- **Pathology**: the disease process affecting the organ, such as coronary artery atheroma or valvular stenosis
- **Impairment**: the negative effect of the pathological process on the function of the organ, such as ischaemia, poor left ventricular function or low cardiac output
- **Disability**: the functional consequences of that impairment for the individual, such as loss of exercise tolerance or chest pain with emotion
- **Handicap**: the effects of that disability on the individual’s role in society, such as unemployment, loss of status or having to give up golf
improvements in blood pressure and lipid profile. Most exercise programmes recommend at least 30 minutes of aerobic exercise three times a week.

The majority of randomised controlled trials of exercise programmes and cardiac rehabilitation have been conducted in patients who have sustained a recent myocardial infarction and indicate that significant morbidity and mortality benefits can be achieved. While the benefits appear to be most prominent in the first 2 years, the secondary preventative effects appear to be sustained over a 10-year period. However, these benefits were only seen when exercise is included as part of multiple lifestyle intervention programmes.

**PQ PATIENT QUESTIONS**

10.37 What is the best way of treating coronary heart disease?
There are many lifestyle changes that can treat coronary heart disease. The most important is stopping smoking. Continued smoking markedly increases the future risk of heart attacks and death. It is the single strongest ‘risk factor’ for future problems with coronary heart disease.

Regular exercise is good for the heart, especially when you have a heart condition. There may be some restrictions on activity but, in general, the more exercise you do, the better shape the heart will be in.

10.38 Is diet important?
Diet is extremely important. It is best to avoid dairy products including butter and cheese. These foods are high in animal fats and increase the risk of heart disease. A diet rich in fruit and vegetables and low in salt and saturated fats has been proven to reduce blood pressure and may well protect against heart disease. In addition, introducing oily fish into the diet and decreasing salt intake will also be of benefit in terms of blood pressure and reducing the risk of heart disease.

If you are overweight, it is sensible to lose weight as this decreases the strain on the heart as well as reducing blood pressure. It may also reduce the likelihood of developing ‘sugar’ diabetes, an important condition that increases the risk of coronary heart disease.

10.39 Is red wine good for the heart?
There is some evidence that drinking red wine in moderation (1–2 glasses per day) can reduce the risk of a heart attack. This could be due to an increase in the good (HDL) cholesterol. However, excessive alcohol intake, especially binge drinking, can increase blood pressure and increase the risk of coronary heart disease. The benefits of moderate alcohol intake are not restricted exclusively to red wine: other forms of alcohol, provided they are
taken in moderation, may also be of benefit in protecting against coronary heart disease.

10.40 Is salt bad for the heart?
Increased salt (>7 g for men and >5 g for women) in the diet can cause an increase in blood pressure which is bad for the heart. For this reason doctors recommend moderate salt intake. In patients with increased blood pressure, it is especially important to keep salt intake low. Furthermore, it is important to recognise that there are ‘hidden’ levels of salt in many processed foods and ready-made meals and patients should read the labels on such products carefully to ascertain how much salt they contain.