CHAPTER 1
Modifying Risk Factors to Improve Prognosis

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OVERVIEW

• Certain personal characteristics and lifestyles point to increased likelihood of coronary heart disease and are called risk factors.
• The three principal modifiable risk factors are smoking, hypercholesterolaemia and hypertension. Other modifiable factors linked to lifestyle include a saturated-fat-rich diet, obesity and physical inactivity.
• Prevention strategies (primary or secondary prevention) aim to reduce the risk of developing or retard the progression of atheroma, to stabilise plaques and to reduce the risk of their erosion or rupture. These measures can collectively reduce the risk of future cardiovascular events (mortality, myocardial infarction and strokes) by as much as 75–80%.
• Percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) revascularisation is not a cure for coronary heart disease and they are predominantly carried out to improve symptoms. They may have little or no prognostic impact in chronic stable angina. However, CABG and PCI confer significant short- and long-term mortality benefit in acute coronary syndromes and, in particular, primary PCI for acute ST segment elevation myocardial infarction.

Table 1.1 Risk factors for the development of premature ischaemic heart disease and acute myocardial infarction

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Modifiable</th>
<th>Not modifiable</th>
<th>RR for AMI</th>
<th>PAR for AMI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Yes</td>
<td>No</td>
<td>2.67</td>
<td>35.7</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>1.91</td>
<td>17.9</td>
</tr>
<tr>
<td>Abnormal lipid levels</td>
<td></td>
<td></td>
<td>3.02</td>
<td>49.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>No</td>
<td>1.91</td>
<td>17.9</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes</td>
<td>No</td>
<td>2.37</td>
<td>9.9</td>
</tr>
<tr>
<td>Male sex</td>
<td>Yes</td>
<td>No</td>
<td>2.0</td>
<td>9.0</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
<td>3.02</td>
<td>49.2</td>
</tr>
<tr>
<td>Psychosocial factors</td>
<td></td>
<td></td>
<td>0.70</td>
<td>13.7</td>
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<tr>
<td>5+ daily fresh fruits/vegetables</td>
<td></td>
<td></td>
<td>0.91</td>
<td>6.7</td>
</tr>
<tr>
<td>Regular alcohol</td>
<td>Yes</td>
<td>No</td>
<td>0.86</td>
<td>12.2</td>
</tr>
</tbody>
</table>

Unmodifiable factors include: hypertriglyceridaemia, lipoprotein (a), microalbuminuria, uric acid, renin, fibrinogen, C-reactive protein and hyperhomocystenaemia.

Notes:
†From STEPS. RR, Relative risk.
††For current and former smokers.
*For AMI, Relative risk for acute myocardial infarction. PAR for AMI (%): Population attributable risk for acute myocardial infarction.

In affluent societies, coronary artery disease causes severe disability and more deaths than any other disease including cancer. It manifests itself as silent ischaemia, angina, unstable angina, myocardial infarction, arrhythmias, heart failure and sudden death. Although this is the result of atheromatous plaque formation and its effect, the actual cause of this process is not known. However, predictive variables – known as risk factors – have been identified which increase the chance of its early development. Risk factors can be classified as modifiable and non-modifiable (Table 1.1).

It is clearly not possible to prevent the increased risk associated with ageing, a positive family history or male gender. However, there are many factors which can be usefully ameliorated by interventions. Moreover, there are some aspects of lifestyle that have been shown to reduce the risk of an acute myocardial infarction.

Risk factors are not simply additive but may be synergistically cumulative. Data from epidemiological surveys have shown for some time that combinations of risk factors generate exponential risks (Figures 1.1 and 1.2). This applies to both men and women. Risk factors are not static but increase with age – this may partly explain the independent effect of age. Blood pressure increases normally with age, so whatever definition is used for hypertension, the frequency of this condition will increase with age. Cholesterol and triglycerides increase with age as do insulin resistance and body mass index.
The beneficial effect of single and combined risk factors on the risk of acute myocardial infarction. Smk, smoking; DM, diabetes mellitus; HTN, hypertension; ApoA1, lipid abnormalities; Obes, obesity; PS, psychosocial factors; RFs, risk factors. From INTERHEART case-control study. Yusuf S et al. Lancet 2004;364:937–52.

The adverse effect of single and combined risk factors on the risk of acute myocardial infarction. By about 2.5 times and reduces absolute survival by, on average, 8 years of follow-up, reinfarction was about 38% in smokers compared with 22% in quitters. Over a 10 years.

Hypertension

Both diastolic and systolic hypertension have been shown to be risk factors for myocardial infarction and cardiovascular death. The relative risk of persistently elevated blood pressure of >160 mmHg systolic is 4 times the risk compared with systolic blood pressure of <120 mmHg.

The relative risk of persistently elevated diastolic blood pressure >100 mmHg is 3 times higher when compared with a diastolic pressure of <80 mmHg. Research data have shown that reduction in diastolic pressure of 5–6 mmHg and systolic pressure of 10–14 mmHg over 5 years with drug therapy does reduce cardiovascular mortality and non-fatal myocardial infarction in elderly people by about 20%, and in younger people by about 14%. Data from the longitudinal epidemiological study in Framingham showed that left ventricular hypertrophy diagnosed by echocardiography is associated with a twofold increased risk in death in women and a 1.5-fold increased risk in men over a 4-year period.

Diabetes mellitus

This is a major risk factor for premature vascular disease, stroke, myocardial infarction and death. Diabetes increases the risk of developing coronary heart disease by 1.5 times at age 40–49 and by 1.7 times at age 50–59 in men and by 3.7 times at age 40–49, and 2.4 times at age 50–59 in women. There are data that show that diabetic control is important for cardiovascular risk, with much more effective risk reduction is associated with aggressive treatment of the commonly associated hypertension, lipid abnormalities and obesity in the diabetic patient.

Obesity

Obesity has been increasing in epidemic proportions and confers a prognostic disadvantage. Those with body mass index (weight/height$^2$) of 25–29 kg/m² are considered to be overweight and those >32 are classified as obese. The latter have a twofold relative increase in mortality from all causes and a threefold increase in cardiovascular death. One study showed that a high body mass index was associated with an increase risk of death per se, especially when it was present in young people aged 30–44 years. More recent evidence suggests that waist circumference is an important independent risk factor as truncal or visceral obesity appears to be more atherogenic. An expanded waist circumference is a necessary criterion for the diagnosis of the metabolic syndrome, in addition to at least two of the other four criteria (Table 1.2).
Despite the presence of the obesity paradox – overweight and obese patients with established cardiovascular disease seem to have a more favourable prognosis than leaner patients – there is data to support purposeful weight reduction in the prevention and treatment of cardiovascular diseases. Furthermore, interventional trials involving bariatric surgery for severe obesity have shown significant weight reduction resulted in significantly reduced mortality.

**Physical activity and fitness**

There is a close inverse relationship between cardiorespiratory fitness and cardiac outcomes such as coronary disease and death. This can be readily assessed by exercise tolerance testing. Patients with a low level of cardiorespiratory fitness have a 70% higher risk for all-cause mortality and a 56% higher risk for coronary or cardiovascular events compared with those with a high level of fitness. Those with intermediate levels of fitness have a 40% higher mortality risk and a 47% higher coronary or cardiovascular event rate than those with higher fitness. Following acute myocardial infarction or coronary artery bypass graft (CABG), cardiac rehabilitation programmes that promote exercise and weight loss can improve cardiometabolic risk profiles of patients.

**Gender**

Men have twice the cardiovascular mortality as women at all ages and in all parts of the world. This was thought to be related to the beneficial effect of female sex hormones, especially oestrogens, as the cardiovascular risk in women increases after the menopause. However, two large randomised controlled trials showed that hormone replacement therapy (HRT) did not reduce the cardiovascular risk in women; rather, the thrombotic effects of oestrogens precipitated fatal and non-fatal cardiovascular events, especially in the early years of treatment. Women appear to possess differently weighted risk factors than men for reasons that are unclear.

More recent data have shown strong associations of accelerated atherosclerosis with low levels of testosterone in men followed up for 4–8 years. Low testosterone level in men has been shown to be linked with increased mortality. Male HRT has not yet been shown to reduce cardiovascular risk, although results from animal studies are encouraging.

**Psychosocial factors**

Some psychosocial factors double the risk of developing cardiovascular disease. Social class has an important effect on mortality from heart disease with people in low-income groups having an excess mortality compared with high-income earners. This is not simply related to deprivation. Within the same working cohort (e.g. Whitehall civil servants), cardiovascular events and mortality were found to be 2–3 times higher in those workers with low socioeconomic status compared with those with high socioeconomic status. In fact, there is little relationship between actual average income and life expectancy. It is not just a matter of money. Mortality is 2–3 times higher in people with poor social links than in those with good social support networks. The reasons are unclear but they are not explained by differences in other known risk factors such as smoking.

**Depression**

Depression carries an adverse prognosis, especially in association with coronary artery disease and is associated with an eightfold increase in cardiovascular death. Patients with depression have a fivefold increased mortality after acute myocardial infarction. There are no data to suggest that treatment of depression with any specific therapy reverses the excess mortality. Depression also influences the outcome after coronary artery bypass surgery. After controlling for age, sex, number of grafts, diabetes, smoking, left ventricular ejection fraction and previous myocardial infarction, moderate or severe depression at the time of surgery increased the risk of death by 2.4 times, and mild to moderate depression that persisted for 6 months conferred a 2.2 times increased risk of death, during a 5-year follow-up period.

**How to assess cardiovascular risk**

Cardiovascular risk stratification is carried out through clinical history, physical examination and serum biomarkers. Following extensive validation, tools such as the Framingham or Reynolds risk scores have been adopted in clinical practice by most primary care practitioners. These scores can identify patients with established risk factors who are at greater risk and would most likely benefit from primary prevention. There are also a number of risk estimates that can be provided electronically from the internet (www.riskscore.org.uk; www.bhsoc.org) that have used large populations on which to base risk assessment. They may have some limitations as they are spot estimates that are critically dependent on age as well as actual measurements of blood pressure and cholesterol – which can fluctuate.

More recently, non-invasive imaging of coronary plaque using cardiac magnetic resonance (CMR) and calcification with measurement of coronary calcium using multislice computed tomography (MSCT) scanning have also been used to identify higher risk populations. However, it is as yet uncertain whether treatment modification in this group will result in improved clinical outcome.

**Effects of drug treatments**

There are two distinct groups of patients who are treated with drug therapy. The first includes those with risk factors for the

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**Table 1.2** International Diabetes Federation definition of metabolic syndrome – focus on waist circumference.

<table>
<thead>
<tr>
<th>Abdominal obesity plus at least two of the following:</th>
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<tbody>
<tr>
<td>Elevated triglycerides</td>
<td>≥1.7 mmol/l</td>
<td></td>
</tr>
<tr>
<td>Reduced HDL-cholesterol</td>
<td>&lt;1.0 mmol/l, 1.3 mmol/l female</td>
<td></td>
</tr>
<tr>
<td>Raised blood pressure</td>
<td>&gt;130/80 mmHg</td>
<td></td>
</tr>
<tr>
<td>Raised fasting plasma glucose</td>
<td>≥5.6 mmol/l</td>
<td></td>
</tr>
</tbody>
</table>

HDL, High-density lipoprotein.
development of premature vascular disease who do not as yet have overt disease, and is categorised as primary prevention. The second includes those patients who have overt cardiovascular disease, such as previous myocardial infarction, peripheral vascular disease and stroke, and is categorised as secondary prevention. The physician must weigh up the risks and benefits of treatment in each individual patient. For example, in patients with overt vascular disease the threshold for drug treatment is much lower because there is a higher benefit to risk ratio from the known drug treatment. In those patients who are at risk but who do not yet have overt disease, the risks may outweigh the benefits especially if the overall likelihood of a cardiovascular event is small. Age has a large effect here as the risk of developing vascular disease increases exponentially over the age of 65. Moreover, the absolute risk of an event increases with age, so decisions about the appropriateness of primary prevention need to be reviewed on a regular basis as the patient ages. There are risk calculators available to help the physician make treatment decisions.

**Aspirin**

Aspirin reduces platelet activation by the inhibition of cyclooxygenase-1 (COX-1) enzyme in platelets, blocking the synthesis of prostaglandin G2/H2 and thromboxane A2. It is the most commonly prescribed drug for the prevention of atherothrombotic events. Its use in patients early after acute myocardial infarction is associated with a reduction in mortality of about 25% (ISIS-2 study). When used in patients with chronic stable angina, there is some evidence that myocardial infarction and sudden death as a combined end point is reduced by about 30%. The benefit is seen almost immediately on starting the drug. However, the benefit of aspirin is to postpone events and not to prevent them. By comparing the event rate in patients taking aspirin and placebo, it is possible to estimate the delay in events conferred by the drug. The average benefit is a delay in event rate of maximum 24 months with aspirin. Aspirin for primary prevention remains controversial as the relatively small benefit is offset by gastrointestinal problems such as bleeding.

**Clopidogrel**

A thienopyridine derivative, clopidogrel prevents adenosine diphosphate (ADP)-mediated activation of platelets, thereby blocking activation of the glycoprotein IIb/IIIa complex. In terms of primary prevention, clopidogrel offers no benefit over aspirin and may even cause harm. In the CHARISMA study, a long-term trial of aspirin combined with clopidogrel versus aspirin alone, there was no significant benefit over aspirin alone and a suggestion of harm in those patients who had risk factors for cardiovascular disease compared with those who had overt disease. However, in patients with overt vascular disease, the drug has been shown to reduce cardiovascular events by about the same degree as aspirin.

In the setting of acute non-ST segment elevation acute coronary syndrome, patients had fewer ischemic end points when treated with the combination of clopidogrel and aspirin compared with aspirin alone, irrespective of whether percutaneous coronary intervention (PCI) was performed or not (CURE study). In the setting of acute ST segment myocardial infarction treated with aspirin and thrombolytic therapy, the addition of clopidogrel for 1 month conferred a small but significant benefit at 1 month (CLARITY and COMMIT studies).

**Cholesterol-lowering drugs**

Statins (3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) inhibitors) have been shown to reduce all-cause mortality and cardiovascular events (acute myocardial infarction, angina, stroke) in both primary and secondary prevention of cardiovascular disease (Figure 1.3).

In a meta-analysis involving over 70,000 patients without established cardiovascular disease but with cardiovascular risk factors, statin therapy was associated with a significant risk reduction in all-cause mortality of 12%, in major coronary events of 30% and in major cerebrovascular events of 19%. Moreover, statin use was not associated with an increased risk of cancer. Statins may have additional antiplatelet and anti-inflammatory benefits. Recently, the JUPITER study showed that rosuvastatin significantly reduced the incidence of major cardiovascular events in apparently healthy people without hyperlipidaemia, but elevated high-sensitivity C-reactive protein (hs-CRP). The proposal that an elevated hs-CRP may be a risk marker or risk factor remains uncertain. Statins have no proven benefit in patients with heart failure. For patients with clinical evidence of cardiovascular disease (previous myocardial infarction or stroke), large-scale trials have indicated that the baseline annual risk of death is about 3%, which is reduced to 2.5% by taking simvastatin. Similarly, long-term registry studies of patients after coronary bypass surgery have shown that average (50%) survival is about 17 years, which is almost 3% per year. In these registry studies, it is also clear that other factors impact on survival after an event – especially the degree of left ventricular damage and the burden of coronary artery disease (number of diseased vessels). Similarly co-morbidity relating to disease in other organ systems adversely affects survival – especially the presence of diabetes and chronic renal dysfunction.
Supplemental treatment with n-3 polyunsaturated fatty acids has also been shown to reduce mortality in patients after acute myocardial infarction, although the effect was small and only 3% of this study population were taking statins at baseline.

**β-Adrenoceptor blocking drugs**

These drugs reduce mortality by about 10–15% at the time of acute myocardial infarction and have also been shown to reduce late mortality after myocardial infarction by about 20–25%. However, in the setting of chronic stable angina there is no evidence that β-blockers reduce the incidence of myocardial infarction or prolong survival.

**Effects of coronary artery revascularisation**

In patients with chronic stable angina, CAGB surgery may improve prognosis in some subgroups of patients, when compared to medical therapy. However, the benefit of this treatment is small. Evidence from rather dated randomised controlled trials of surgery versus medical treatment has shown the following:

- **Patients with significant left main stem stenosis**: Survival over a 10-year period was increased by an average of 19 months.
- **Patients with significant stenoses of three vessels**: Survival was extended by about 6 months.
- **Patients with single or two significant coronary artery stenoses**: Survival was extended by only 1 month.
- **Patients with impairment of left ventricular function**: Survival was extended for about 8 months longer after surgery.

The recent SYNTAX trial of patients with severe coronary artery disease (including severe left main stem disease) showed that at 1 year, CAGB was superior to PCI in terms of composite outcome of death, myocardial infarction, stroke and repeat interventions. Repeat revascularisation was significantly higher in the PCI group, and most of these patients were treated with PCI rather than CAGB. However, mortality per se was similar in both groups (4.4% PCI vs 3.5% CABG) and the stroke rate was nearly 4 times higher in the CAGB group (2.2% vs 0.6% PCI). Longer term follow-up may further clarify the relative benefits of these two procedures.

In patients with acute coronary syndromes (unstable angina, non-ST segment elevation myocardial infarction and ST segment elevation myocardial infarction), the combined endpoint of myocardial infarction and mortality is reduced by timely interventional therapy. A review of the clinical trial evidence shows that those patients at highest risk benefit most. In the setting of acute ST segment elevation myocardial infarction, a meta-analysis has shown that primary PCI confers significant mortality and recurrent myocardial infarction benefits.

**Conclusion**

Although cardiovascular disease continues to exert major socio-economic consequences, there has been a substantive fall in death rates from coronary heart disease over the past decades. Recent evidence highlights the crucial impact of risk factor modification by way of primary and secondary prevention, revascularisation strategies, as well as the modern care of acute coronary syndromes, which incorporates early PCI/CABG policies. The dividing wall between secondary and primary prevention appears to be less significant than before as emerging data highlights the trend towards multiple risk factor modification for all groups. As lowering all risk factors simultaneously has a multiplicative effect in reducing risk, some groups are exploring the interesting potential of a single, multi-drug tablet (referred to as the polypill). This will include aspirin and a lower dose statin, an ACE inhibitor and a β-blocker for all those above 55 years, diabetics above 35 years and any ages in those with known coronary artery or cerebrovascular disease.

**Further reading**


