Cardiovascular disease (CVD) is currently the leading cause of morbidity and mortality worldwide and its incidence is likely to increase. Multiple risk factors contribute to CVD. Elevated LDL-cholesterol (LDL-C) and triglyceride levels, low HDL-cholesterol levels, hypertension, type 2 diabetes, and smoking are key modifiable risk factors. Such risk factors are present in 80–90% of coronary heart disease (CHD) patients. For many factors, modification can significantly reduce CVD incidence. For example, statin-induced LDL-C reductions reduce cardiovascular events by 24–37% and smoking cessation reduces CHD mortality by 36%. The need to identify and treat these risk factors has led many national and local groups to develop clinical practice guidelines for management of CVD. Although the aim of such guidelines is to provide practitioners with a framework to identify, prioritize, and manage patients, the plethora of guidelines can cause confusion. In addition, research indicates that guidelines are not being optimally implemented. This review considers these practical issues, highlights the common goals shared by many guidelines, and focuses on how these can be best achieved. It also highlights areas where the guidelines differ and discusses points to consider when selecting the most appropriate recommendation.

Guideline implementation: the clinical reality

The effectiveness of guidelines lies in their appropriate selection and subsequent implementation. However, owing to the large number of guidelines available, this can be time consuming and confusing. Recent surveys indicate that guidelines awareness and acceptance is high among practitioners, but that implementation could be improved.1,2

In a recent survey of European primary care practitioners, 89% agreed with European societies guidelines, but only 18% believed that they were being adequately implemented.2 Studies confirm this belief. Plasma lipid levels are not screened in many at-risk patients3,4 and, in patients receiving treatment, risk factor management can be poor.1,5,6 The European Action on Secondary Prevention through Intervention to Reduce Events survey5 showed a high prevalence of uncontrolled dyslipidaemia, hypertension, obesity, and smoking in patients with established coronary heart disease (CHD) (Table 1).5 In European and American studies, most high-risk patients’ cholesterol levels exceed recommended goals.1,5

Potential reasons for not reaching cholesterol targets include suboptimal therapy (inadequate drug dosage/lack of titration), underuse of statin therapy (medication not prescribed or not taken), and concerns regarding side-effects of medication.1,5,7–10 Practitioners cite lack of time, prescribing costs, and patient non-compliance as barriers to implementation.2 However, correct implementations of guidelines could reduce cardiovascular disease (CVD) morbidity and mortality.

Guidelines: the common goals

Table 2 highlights the similarities shared by some of the key CVD prevention and management guidelines.11–19

The importance of patient screening and identification

All guidelines provide advice on screening and identifying asymptomatic patients at risk of developing CVD, thus highlighting the importance of this initial step. Opportunities to screen patients exist within daily clinical practice (Table 3).

The need to calculate total risk

All guidelines provide a system to calculate risk. The general principle is to assign points to patients according to their risk factor exposure. The sum of these points is used to calculate patients’ total risk (Table 4).

All the guidelines focus on multiple risk factors. They agree that risk factors increase the likelihood of a cardiovascular (CV) event and that risk is additive. The compound
Table 1 EUROASPIRE\textsuperscript{5}—Prevalence of risk factors in patients with established CHD

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High total cholesterol</td>
<td>58.8</td>
</tr>
<tr>
<td>([\geq 194 \text{ mg/dL (} \geq 5 \text{ mmol/L)}])</td>
<td></td>
</tr>
<tr>
<td>High blood pressure</td>
<td>53.9</td>
</tr>
<tr>
<td>((\text{SBP} \geq 140 \text{ mmHg and/or DBP} \geq 90 \text{ mmHg}))</td>
<td></td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30 kg/m\textsuperscript{2})</td>
<td>32.8</td>
</tr>
<tr>
<td>Smoking</td>
<td>20.8</td>
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</tbody>
</table>

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BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

effect of risk factors is illustrated by data from the Framingham Study (Figure 1). Data from patients with type 2 diabetes and/or the metabolic syndrome (in whom CVD risk factors tend to cluster) support this concept: in a sub-study of the Botnia trial, presence of the metabolic syndrome was associated with relative risks of 3.0, 2.6, and 1.8 for CHD, myocardial infarction (MI), and CVD mortalities, respectively. Similarly, diabetes is associated with a two- to five-fold increase in the risk of MI.

Tools are available to assist practitioners in an office-based assessment of patients. The Framingham risk equation and SCORE risk chart are now widely available in paper and electronic formats.

The significance of risk reduction

Once an individual’s risk has been estimated, CVD prevention relies on implementing effective risk management programmes. Guidelines provide recommendations on appropriate treatment for different risk levels.

The guidelines agree that high-risk patients are a priority (Table 5). Most guidelines recommend initiating lifestyle changes and lipid-modifying drugs simultaneously in this group, and treatment goals are generally similar among guidelines (Table 2). Anti-hypertensive and anti-hyperglycaemic agents (as appropriate) are also important for these patients. All guidelines recommend regular monitoring of high-risk patients.

There is also agreement among guidelines on treatment recommendations for low-risk patients. Lifestyle changes including diet, exercise, and weight loss should be implemented in these patients, who should receive regular follow-up (every 1–5 years).

In assessing risk and recommending preventive management, most guidelines have a relatively short-term focus, i.e. the next 5 or 10 years. Individuals with the highest short-term risk are then recommended for the most intensive interventions. However, atherosclerosis is a chronic condition that usually commences decades before it elicits a CV event. It might therefore be more beneficial to consider life-time risk and to identify and target at-risk individuals before they reach high-risk status. Early institution of intensive preventive treatment in these individuals at longer term risk has the potential to substantially reduce CV risk in later life. The presence of asymptomatic atherosclerosis may be identified by non-invasive tests such as ankle-brachial index measurement, carotid ultrasonography, or exercise stress testing.

Guidelines: areas of divergence

Which factors are most important in determining total risk?

The guidelines agree on the need to assess total risk, but differ on the selection and weighting of risk factors. Many guidelines focus on LDL-cholesterol (LDL-C) as the primary target. Others, however, utilize HDL-cholesterol (HDL-C) and total cholesterol. Inclusion of HDL-C reflects growing recognition of the atheroprotective properties of this lipoprotein fraction. These differences in weighting can alter risk predictions and treatment recommendations for individual patients (Table 6), particularly in primary prevention. In a recent comparison involving individuals without clinical evidence of CVD, NCEP ATP III and European guidelines recommended institution of lipid-modifying therapy in 52 and 26% of patients, respectively.

An alternative estimator of risk, advocated by the Canadian guidelines, is apolipoprotein B. This lipoprotein, which is present in all atherogenic particles and thus reflects total atherogenic load, may be particularly useful for estimating risk in individuals with hypertriglyceridaemia. In four recent prospective studies, apolipoprotein B was a better estimator of CV risk than LDL-C.

Which algorithm is most appropriate for estimating risk?

Risk charts derived from Framingham data that calculate the 10 year risk of MI and CHD mortalities have been incorporated into numerous guidelines (Table 2). The Framingham algorithm estimates risk accurately in European and American populations that have an average CHD risk similar to the Framingham cohort (a US population). However, this algorithm over-estimates risk in populations with a lower baseline risk, such as those in France, Italy, and Spain. Recalibration of the Framingham data set is possible, but may be difficult in the clinical setting.

The European guidelines have abandoned the Framingham risk equation in favour of the European Systematic Coronary Risk Estimation (SCORE) model. On the basis of a large data set from several European cohorts, this model has separate risk charts for low- and high-risk regions of Europe. This avoids overestimation of CHD rates in low-risk populations that can occur when using risk equations developed using data from high-risk populations, such as the Framingham cohort. The SCORE charts assess 10 year risk of total CVD mortality (CHD, peripheral arterial disease and ischaemic stroke), whereas the Framingham equation assesses fatal and non-fatal CHD.

The SCORE charts can be used to project risk to 60 years and allow relative risk to be assessed, which can be useful in demonstrating the importance of risk factor management to patients, and enable countries with no cohort studies to choose the most appropriate model after calculation of baseline risk from national mortality data. National/regional charts are also in development.

What constitutes a risk threshold?

Guidelines are generally in agreement on the treatment approach for high- and low-risk patients, but there is some divergence regarding the risk level at which drug therapy
Table 2  Summary of guideline characteristics: areas of convergence and divergence

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<tbody>
<tr>
<td>Data set Screening</td>
<td>Framingham</td>
<td>SCORE Risk assessment every 5 years; complete lipid profile if 10 years risk ≥ 5%</td>
<td>Framingham Risk assessment of all adults; lipid screen: high-risk and adults ≥ 45 years every year</td>
<td>Framingham Risk assessment: asymptomatic men 45 years (or ≥ 35 years with risk factors); asymptomatic women ≥ 55 years (or ≥ 45 years with risk factors)</td>
<td>Framingham Adults aged 35–69 with risk factors: lipid screen after MI</td>
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<td>Not specified</td>
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<tr>
<td>Risk factors assessed</td>
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<td>Diabetes/IGT</td>
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<tr>
<td>Points assigned</td>
<td>In CHD or CHD equivalents: LDL-C &lt; 100 mg/dL (2.6 mmol/L); optional goal LDL-C &lt; 70 mg/dL (&lt; 1.8 mmol/L) for very high risk patients</td>
<td>In CVD patients and diabetes patients: TC &lt; 4.5 mmol/L; LDL-C &lt; 2.5 mmol/L; Asymptomatic patients: TC &lt; 5 mmol/L; LDL-C &lt; 3 mmol/L</td>
<td>In secondary prevention: LDL-C &lt; 2.5 mmol/L; TC &lt; 4.0 mmol/L; HDL-C &gt; 1.0 mmol/L; TG &lt; 2.0 mmol/L</td>
<td>In primary prevention: LDL-C &lt; 3.0 mmol/L</td>
<td>In secondary prevention: LDL-C &lt; 2.5 mmol/L; TC &lt; 4.0 mmol/L; HDL-C &gt; 1.0 mmol/L; TG &lt; 1.7 mmol/L</td>
<td>No recommendation provided for primary prevention</td>
<td>Points assigned in High-risk patients: LDL-C &lt; 2.5 mmol/L and TC:HDL-C ratio &lt; 4.0 or: apolipoprotein B &lt; 0.9 g/L Moderate-risk patients: LDL-C &lt; 3.5 mmol/L and TC:HDL-C ratio &lt; 5.0 or: apolipoprotein B &lt; 1.05 g/L Low-risk patients: LDL-C &lt; 4.5 mmol/L and TC:HDL-C ratio &lt; 6.0 or: apolipoprotein B &lt; 1.2 g/L</td>
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Continued
is recommended. This results in a group of intermediate-risk patients for whom treatment strategies are poorly defined. Data are emerging, which support the use of additional factors such as C-reactive protein, non-HDL-C, fibrinogen, lipoprotein(a), and apolipoprotein B in determining risk. These parameters, and the other non-invasive tests discussed earlier, may prove particularly useful for stratifying intermediate-risk patients.

Who should be treated?

It is important that guidelines are based on up-to-date clinical data. The recent NCEP ATP III guidelines update\(^{13}\) is based on results of five major clinical trials of statin therapy conducted since the 2001 guidelines\(^{11}\) were released. The trials support many NCEP ATP III recommendations, including the use of LDL-lowering therapy in diabetic patients and older persons. In addition, they have shown the benefits of LDL-lowering therapy in patient groups for which ATP III could not make definitive recommendations and have demonstrated the efficacy of risk reduction in high-risk persons with relatively low LDL-C levels. As a result, the NCEP update recommends an optional therapeutic target of LDL-C \(\leq 70\) mg/dL (1.8 mmol/L) in very high risk patients: those with acute coronary syndrome or those with CHD plus diabetes, the metabolic syndrome, multiple-risk factors, or a poorly controlled risk factor (e.g. continued smoking).\(^{13}\) Studies have demonstrated benefit from lipid lowering irrespective of initial LDL-C levels, including those with average levels at baseline. Indeed, LDL-C levels as low as 1.8 mmol/L have been shown to be protective in high-risk individuals in clinical trials.\(^{13}\)
The major recommendations for modifications to the ATP III treatment algorithm are summarized in Table 7.

The use of statins, beta-blockers, and angiotensin-converting enzyme-inhibitors is widely recommended for patients with symptomatic CHD, regardless of cholesterol or blood pressure levels.12,15,17,32 However, for patients who are already below target levels before treatment, recommending therapeutic lipid and blood pressure goals is of no value. In such situations, it may be more appropriate to recommend drug dosages rather than risk factor targets. This approach is taken by the Canadian guidelines,19 which recommend that all high-risk individuals should receive the equivalent dose of 40 mg/day simvastatin. A similar approach is taken by the Australian Practical Implementation Taskforce for the Prevention of CVD,33 which recommends that all patients with CHD should receive ramipril (10 mg) or perindopril (8 mg), regardless of blood pressure. Publication of separate recommendations for high-risk symptomatic and asymptomatic individuals might reduce the confusion generated by recommending lipid and blood pressure targets for populations that should receive treatment regardless of risk factor level.

Some guidelines highlight certain ethnic groups that have a higher CV risk (Table 8) than the general population. Advice on assessing other patient groups such as those with the type 2 diabetes and/or the metabolic syndrome is also given by most guidelines, although risk assessment and treatment recommendations may differ. The NCEP ATP III guidelines11,13 define diabetic patients as CHD equivalents, i.e. their CHD risk is considered equal to that of an individual with established CVD. The New Zealand15 and Australian14 guidelines use separate tables for assessing risk in these patients, although the European12 guidelines assume that the presence of type 2 diabetes doubles the baseline risk in men and quadruples the risk in women.

The effect of gender on CV risk is acknowledged by all guidelines. Most recommendations for CVD prevention and treatment are similar for men and women, although gender-specific issues (e.g. use of hormone replacement therapy) do exist. The recent publication of evidence-based guidelines for CVD prevention in women provides a comprehensive summary of this topic.32

Individuals with the metabolic syndrome constitute a population whose risk is not easily quantified using standard algorithms, and therefore guidelines generally recommend that these patients’ 10 year risk should be adjusted upwards. However, accurate risk assessment is further complicated by the diversity of metabolic syndrome definitions. The most widely accepted criteria are those of the World Health Organization (WHO)34 and the NCEP.11 The latter definition is more widely used.

Which therapeutic targets are the most appropriate?

Although most guidelines recommend reduction of total cholesterol and LDL-C, evidence is accruing to support the use of other therapeutic targets. The NCEP ATP III guidelines11,13 use non-HDL-C (LDL-C + VLDL-C) as a target for individuals in whom triglycerides exceed 2.3 mmol/L. This recommendation acknowledges the atherogenic potential of triglyceride-rich remnant lipoproteins, which are most readily measured as VLDL-C.8 The Canadian guidelines19 regard apolipoprotein B as an alternative therapeutic target for patients at all levels of risk.
because, once a statin has been prescribed, titration is unimportant that an optimal dose is used from the outset depending on the statin) fail to achieve their LDL-C goal of 20–30% with pravastatin (10–40 mg). In a separate study, patients, conduct ongoing monitoring, and choose the most effective therapies and drug dosages. However, drug dosage is a topic on which the guidelines give little guidance. The Atorvastatin Comparative Cholesterol Efficacy and Safety Study showed that most CHD patients (47–85%, depending on the statin) fail to achieve their LDL-C goal of ≤100 mg/dL (2.6 mmol/L) at starting statin doses. It is important that an optimal dose is used from the outset because, once a statin has been prescribed, titration is unlikely to occur. The recent ATP III update recommends that all high-risk patients should start on a statin dose that provides ≥30–40% reduction in LDL-C. The update provides a table to guide clinicians in selecting the appropriate dose of each statin (Table 9). This shows that statins differ widely in potency. In a study of 2431 mild to moderately hypercholesterolaemic patients, LDL-C was reduced by 20–66, and 2–22% with atorvastatin, simvastatin and pravastatin, respectively. In primary care, non-compliance with statin therapy occurs commonly (15–52% of patients). Patients may discontinue treatment because of poor efficacy or adverse events. Myopathy is the most common and potentially the most serious adverse effect of statin therapy. It is, however, rare. In a study involving 218 892 person-years of statin mono- and combination therapy, the average incidence of hospitalized rhabdomyolysis was 0.44 per 10 000 person-years of monotherapy with atorvastatin, pravastatin, or simvastatin. Since statin monotherapy reduces CV risk by ~35% in individuals at low or high risk, patients with baseline 10 year risks of 5 and 20% have annual CV risks of ~0.33 and 1.3%, respectively, if assigned to statin therapy. The risk–benefit ratio is thus firmly in favour of statin use.

Primary care practitioners can improve compliance and persistence through regular monitoring and by educating and motivating patients. Potential interventions include one-to-one discussions, written materials, telephone follow-up, and group sessions. Individual counselling and community initiatives are effective in achieving lifestyle changes and reducing LDL-C levels. One of the most successful community-based programmes is the Finnish North Karelia project. Its success in reducing CVD risk factors led to the development and implementation of a national CVD prevention strategy in the 1970s. This has significantly lowered cholesterol, blood pressure, and smoking levels nationwide. A European-wide initiative, EUROACTION, is currently investigating whether the Second Joint European Societies guidelines on lifestyle, risk factor, and therapeutic goals for CVD can be realized in everyday practice through a multi-disciplinary team comprising cardiologists, primary care practitioners, specialist nurses, dieticians, and physiotherapists.

Conclusion

Primary care practitioners are in a pivotal position to improve CVD management, and guidelines can assist in meeting this challenge. The numerous guidelines available contain many similarities. All guidelines promote screening and identification of at-risk patients. They concur that risk factors increase CV risk in a compound manner.
treatment and follow-up regimens for different risk levels. The advice provided by different guidelines is similar for secondary prevention and for high- and low-risk patients. However, there are areas in which the guidelines differ, including the selection and weighting of risk factors, risk algorithms, and treatment thresholds. Divergence of the guidelines is greatest for primary prevention in intermediate-risk patients.

Countries that have not developed their own guidelines may consider using those of the International Atherosclerosis Society. This document, which represents an attempt to harmonize existing guidelines, highlights the differences inherent in producing a 'one size fits all' solution to the problem of CVD prevention, and acknowledges the substantial differences among countries in baseline risk, medical expenditure, and healthcare priorities. Ultimately, physicians in each region must decide which guidelines best reflect the medical priorities and CV risk profile of the population for which they are responsible.

Acknowledgements

C.B. has received research grants and consulting honoraria from AstraZeneca, Pfizer, Merck, Schering-Plough, Novartis, and Kos Pharmaceuticals. B.A. has received educational sponsorship from AstraZeneca. J.S. has received educational sponsorship from AstraZeneca, Merck AG, MSD, BMS, Schering Plough and GSK. Editorial support was provided by The Future Forum Secretariat, London, UK.

References


Table 8 Ethnic groups at high risk according to guidelines
Aboriginal peoples and Torres Strait Island: Australian guidelines recommend screening lipids
Māori, Pacific peoples, and people from the Indian subcontinent: New Zealand guidelines recommend adding 5% to their risk and to start screening 10 years earlier.

Table 9 Statin dose required to attain approximate 30–40% reduction in LDL-C levels

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/day)</th>
<th>LDL reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>5–10×</td>
<td>39–45</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10×</td>
<td>39</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>20–40×</td>
<td>35–41</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>40×</td>
<td>31</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>40×</td>
<td>34</td>
</tr>
<tr>
<td>Fluvasstatin</td>
<td>40–80</td>
<td>25–35</td>
</tr>
</tbody>
</table>

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×Doses available up to 40 mg.
bEfficacy for 5 mg estimated by subtracting 6% from Food and Drug Administration–reported efficacy at 10 mg. A 5 mg dose licensed in USA and in Europe for patients with predisposing factors for myopathy.
×Dose available up to 80 mg.


