Prediction of coronary risk for primary prevention of coronary heart disease: a comparison of methods

I.U. HAQ, L.E. RAMSAY, P.R. JACKSON and E.J. WALLIS

From the Department of Clinical Pharmacology and Therapeutics, Royal Hallamshire Hospital, Sheffield, UK

Received 23 April 1999

Summary

Most recent guidelines advise targeting of lipid lowering for primary prevention at those at high absolute coronary (CHD) risk. We compared the accuracy of five CHD risk assessment methods in identifying such patients: one based on total cholesterol \( \geq 6.5 \text{ mmol/l} \) plus two risk factors, and four based on the Framingham risk function (the European Task Force chart and Sheffield table, both using total cholesterol and the New Zealand chart and modified Sheffield table, both using total : HDL cholesterol ratio) for predicting CHD event risk \( \geq 2\% \) per year, calculated by an independent risk function, PROCAM, in 126 treated hypertensive men. Cholesterol threshold plus two risk factors had sensitivity 59\% and specificity 63\%, did not identify some very high-risk patients, and identified very low-risk patients. Framingham-based methods using total cholesterol alone had sensitivity 90–98\% and specificity 37–43\%, and identified high-risk patients well, but identified some patients at very low risk. Methods based on total : HDL cholesterol ratio had sensitivity 90–98\% and specificity 60–63\%, and did not identify incorrectly patients at very low CHD risk. Methods based on cholesterol threshold and counting of risk factors are too inaccurate for targeting drug therapy for primary prevention of CHD. Framingham-based methods should incorporate HDL-cholesterol as the total : HDL cholesterol ratio.

Introduction

Recent outcome trials with HMG Co-A reductase inhibitors (statins) have radically changed therapeutic policies for cholesterol reduction. Secondary prevention in those with established coronary or atherosclerotic disease and serum cholesterol \( \geq 5.0 \text{ mmol/l} \) is accepted as the first priority.\(^1\)\(^2\) However, guidance on statin treatment for primary prevention of coronary heart disease (CHD) is not uniform.\(^3\) When recommendations of the British Hyperlipidemia Association,\(^4\) European Joint Task Force,\(^5\) US National Cholesterol Education Program\(^6\) (NCEP), or a Standing Medical Advisory Committee\(^7\) (SMAC) are applied to British adults, they identify for treatment as few as 3.7\% or as many as 13.5\% of the population.\(^3\) Moreover, the individuals identified by the different guidelines are not the same.\(^3\) These inconsistencies could reflect differences in interpreting the evidence, differences in policy, or differences in methods of implementing policy.\(^8\) Interpretation of the evidence on statin treatment appears straightforward. Statins reduce major CHD events by 33\% in those with LDL-cholesterol \( > 3.2 \text{ mmol/l} \), and the relative risk reduction is constant between trials and in subgroups within trials.\(^5\)\(^10\) A constant relative risk reduction means that benefit from treatment is related to the absolute CHD risk. Absolute CHD risk therefore determines benefit to the individual (NNT), cost-effectiveness, the proportion of the population treated, and the total cost of statin treatment.\(^9\)\(^11\) A general consensus that statin treatment should be targeted at absolute CHD risk\(^12\) is echoed in all recent guidelines.\(^1\)\(^2\)\(^5\)\(^7\)

The guidelines differ principally in the policies set for treatment, and on methods of identifying people
to be treated. Two of them advise treatment based on thresholds of total or LDL-cholesterol plus counting of additional risk factors such as smoking, diabetes or hypertension. They do not state explicitly the CHD risk threshold identified, but it equates to a CHD event risk of approximately 2% per year, at least in middle-aged men. The European Joint Task Force also uses total least in middle-aged men.

The method of identifying people for treatment is based on the additional CHD risk factors, with age and Sheffield. The emphasis should be to identify best those with the level of absolute CHD risk that warrants treatment? The method selected needs to be simple for acceptance in ordinary practice, accurate, and valid for estimating absolute CHD risk. When considering accuracy the balance between sensitivity and specificity is important. Statin treatment for primary prevention might now be justifiable on harm–benefit criteria at a CHD event risk as low as 0.6% per year. The emphasis should therefore be to identify and treat all those above the specified CHD risk threshold because no harm will come from treating ‘incorrectly’ those below that threshold, provided their CHD risk is not very low. The method of identifying people for treatment should therefore have high sensitivity, with some sacrifice of specificity if necessary. We have compared the accuracy of five methods for estimating absolute CHD risk, one using a cholesterol threshold plus simple counting of risk factors, and four based on the Framingham risk function. Two of the Framingham-based methods use total cholesterol only (European Joint Task Force chart and Sheffield table), and two use the total: HDL cholesterol ratio (New Zealand chart and modified Sheffield table). The validity of risk estimates based on the Framingham function was examined by comparing them to estimates of CHD risk by the PROCAM risk function, which is derived from a prospective study in a German population.

### Methods

**Risk assessment methods**

The European Joint Task Force chart estimates CHD risk using age, sex, systolic blood pressure, smoking and total cholesterol. The original Sheffield table used the same variables plus diabetes and left ventricular hypertrophy on ECG. In an updated Sheffield table, serum total: HDL cholesterol ratio replaces total cholesterol. The New Zealand chart also uses total: HDL cholesterol ratio and these other risk factors, but estimates cardiovascular event risk rather than CHD event risk. The method for cholesterol threshold plus counting of risk factors was that used in a subgroup analysis of WOSCOPS, requiring a total cholesterol ≥ 6.5 mmol/l plus any two additional CHD risk factors, with age > 55 years in men counted as one risk factor. This is similar to recommendations by the British Hyperlipidemia Association and American National Cholesterol Education Program, although the latter is based on LDL-cholesterol rather than total cholesterol. The European and threshold plus counting methods cannot target a CHD event risk of 3% per year, and for the purpose of this analysis the Sheffield tables were recast to target a CHD event risk of 2% per year. The CHD risk of each patient was estimated using all five risk assessment methods in accordance with published instructions on their use. The external standard was CHD risk calculated by the full PROCAM risk function using age, blood pressure, smoking, diabetes, total and HDL-cholesterol, and family history. This analysis was restricted to men, because CHD risk in women could not be calculated by PROCAM at the time. CHD event risk was also calculated for men and women using the full Framingham risk function.

**Patients**

Complete data to enable calculation of CHD risk by the PROCAM and Framingham risk functions were collected prospectively for 216 consecutive treated hypertensive patients who were aged 35–70 years, had total cholesterol ≥ 5.5 mmol/l, and were free of vascular complications by clinical evaluation or ECG. The variables measured and recorded were age, sex, smoking habit and family history (both by structured questions), blood pressure (mean of two measurements), diabetes (fasting glucose > 7.8 mmol/l, or treated), and ECG left ventricular hypertrophy by criteria used in Framingham. The characteristics of the study population are shown in Table 1. The mean CHD event risk calculated by the full Framingham function was 2.5% (SD 1.2%) per year in men.
Table 1  Mean (SD) data used for CHD risk assessment in 216 hypertensive patients

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>Men and women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>126</td>
<td>90</td>
<td>216</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.7 (7.2)</td>
<td>59.2 (6.7)</td>
<td>58.9 (7.0)</td>
</tr>
<tr>
<td>Systolic blood pressure(mmHg)</td>
<td>149 (12.2)</td>
<td>152 (10.5)</td>
<td>150 (11.6)</td>
</tr>
<tr>
<td>Cigarette smokers (%)</td>
<td>19</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>9</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Family history of CHD (%)</td>
<td>34</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>Serum total cholesterol(mmol/l)</td>
<td>6.6 (0.87)</td>
<td>6.8 (0.96)</td>
<td>6.7 (0.91)</td>
</tr>
<tr>
<td>Serum HDL-cholesterol (mmol/l)</td>
<td>1.1 (0.32)</td>
<td>1.3 (0.38)</td>
<td>1.2 (0.36)</td>
</tr>
<tr>
<td>Total: HDL cholesterol ratio</td>
<td>6.46 (1.73)</td>
<td>5.58 (1.72)</td>
<td>6.09 (1.78)</td>
</tr>
<tr>
<td>Left ventricular hypertrophy (ECG) (%)</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>CHD risk by Framingham equation (% per year)</td>
<td>2.45 (1.17)</td>
<td>1.35 (0.87)</td>
<td>1.99 (1.19)</td>
</tr>
<tr>
<td>Number (percentage) with risk ≥2% per year by Framingham equation</td>
<td>79 (63%)</td>
<td>16 (18%)</td>
<td>95 (44%)</td>
</tr>
<tr>
<td>Number (percentage) with risk ≥3% per year by Framingham equation</td>
<td>38 (30%)</td>
<td>4 (4%)</td>
<td>42 (19%)</td>
</tr>
<tr>
<td>CHD risk by PROCAM equation (% per year)</td>
<td>2.27 (1.71)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Number (percentage) with risk ≥2% per year by PROCAM equation</td>
<td>63 (50%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Number (percentage) with risk ≥3% per year by PROCAM equation</td>
<td>35 (28%)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

(n=126); 1.4% (0.9%) per year in women (n=90); and 2.0% (1.2%) per year for all subjects.

Analysis

The principle endpoint was the accuracy of the different risk assessment methods in men for predicting a CHD event risk ≥2.0% per year calculated by the full PROCAM risk function. The predictive value of HDL-cholesterol (in the total: HDL cholesterol ratio) was examined further by comparing the accuracy of Sheffield tables based on total cholesterol alone (using population mean values for HDL-cholesterol) or the total: HDL cholesterol ratio for estimating CHD event risk ≥3.0% per year calculated by the full Framingham risk function. Sensitivity, specificity and 95%CIs were calculated by standard methods.21

Results

Comparison of methods

The sensitivity and specificity for each method, and the mean CHD event risks in those treated or not treated, are shown in Table 2. The method based on cholesterol threshold ≥6.5 mmol/l plus two CHD risk factors had a sensitivity of 59% and specificity 63% versus PROCAM, with mean annual CHD event risk of 2.7% for those treated and 1.9% for those not treated. All four methods based on Framingham had sensitivity between 90–98% for predicting a CHD event risk of 2% per year by PROCAM. Those based on total cholesterol alone5,10 had lower specificity (37% and 43%) than those using the total: HDL cholesterol ratio18,19 (60% and 63%). The two methods based on total: HDL cholesterol ratio18,19 identified men with a mean CHD event rate of 3.0% per year for treatment, and with rates of 0.7 and 1.0% per year in those not treated. The scatter for the cholesterol threshold plus risk factor counting method and the Sheffield tables based on total cholesterol or the total: HDL cholesterol ratio are shown in Figure 1. The cholesterol threshold plus risk factor counting method failed to treat patients with high and even extremely high CHD risk, and often identified for treatment patients at very low CHD risk, below 0.6% per year. This method failed to classify five men for treatment despite them actually having an annual CHD risk >5% by the PROCAM function. These men had serum cholesterol <6.5 mmol/l but had numerous other risk factors. All five men were >60 years old; three had systolic blood pressure ≥160 mmHg; two were smokers; four were diabetic; three had a positive family history of ischaemic heart disease; and four had serum HDL concentration ≤1.0 mmol/l. The table based on total cholesterol alone failed to treat some patients above the 2% per year threshold, and also treated patients with CHD risk below 0.6% per year. The table incorporating HDL-cholesterol in the ratio treated almost all patients with CHD event risk ≥2% per year, and did not treat any patient with CHD risk below 0.6% per year.
Table 2  Sensitivity and specificity (and 95% CIs) of methods for identifying a CHD event risk ≥2% per year by the PROCAM risk function in 126 men

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Mean CHD event risk (%/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥6.5 mmol/l plus two risk factors</td>
<td>59 (47–71)</td>
<td>63 (52–75)</td>
<td>2.7</td>
</tr>
<tr>
<td>Euro Task Force (TC)</td>
<td>98 (95–100)</td>
<td>37 (25–48)</td>
<td>2.6</td>
</tr>
<tr>
<td>Sheffield Table (TC)</td>
<td>90 (83–98)</td>
<td>43 (31–55)</td>
<td>2.6</td>
</tr>
<tr>
<td>Sheffield Table (TC; HDL)</td>
<td>97 (92–100)</td>
<td>60 (48–72)</td>
<td>3.0</td>
</tr>
<tr>
<td>NZ Chart (TC; HDL)</td>
<td>90 (83–98)</td>
<td>63 (52–75)</td>
<td>3.0</td>
</tr>
</tbody>
</table>

TC, total cholesterol; TC; HDL, total: HDL cholesterol ratio; NZ, New Zealand.

Importance of total : HDL cholesterol ratio

Figure 2 shows the outcome of targeting a CHD event risk of 3% per year, calculated by the full Framingham function, using Sheffield tables based on total cholesterol alone or the total : HDL cholesterol ratio in men and women combined. The latter table incorporates all the variables in the Framingham risk function, with only blood pressure approximated, and as anticipated the sensitivity (100%) and specificity (94%) are very high. Those identified for treatment have a mean CHD event risk much higher than that of those untreated (4.1% vs. 1.8% per year). Use of total cholesterol alone also identifies high (3.6%) and low (1.5%) risk groups, has no important effect on specificity (98%), but reduces the sensitivity markedly to 45%. Virtually all those treated have a CHD event risk ≥3% per year, but it fails to treat many patients who are above the preset threshold. Most but not all of the high-risk men not treated have CHD event risks between 3–4% per year.

Discussion

The Framingham risk function has been available for several years, but was used little in ordinary practice until recently. In Britain a national survey of local policies for cholesterol management in 1994 showed that only 2% included a formal risk assessment method. However, methods based on Framingham are now in widespread use. Reasons include acceptance that individual benefit, cost-

Figure 1. Outcome of targeting treatment at a CHD event risk ≥2.0% per year calculated by the PROCAM risk function in 126 men, using a total cholesterol > 6.5 mmol/l plus two CHD risk factors; b Joint European Task Force recommendations; c Sheffield table based on total cholesterol; d Sheffield table based on total: HDL cholesterol ratio; e New Zealand risk chart.
Predicting CHD for primary prevention

383

Figure 2. Outcome of targeting treatment at a CHD event risk \( \geq 3.0\% \) per year calculated by the Framingham risk function in 126 men and 90 women, using a Sheffield table based on total cholesterol; b Sheffield table based on total:HDL cholesterol ratio.

effectiveness, volume and total cost of statin treatment are determined by absolute CHD risk;\(^5,7\) and wide dissemination of simple Framingham-based methods in national and international guidelines.\(^1,5,7,14,18,19\) Absolute CHD risk is the correct starting point when considering statin treatment, not thresholds of cholesterol or other lipid fractions.\(^9,23\) Moreover, intuitive or informal assessment of absolute CHD risk by doctors is highly inaccurate.\(^24\) Without formal risk assessment, prescribing policies are very inconsistent, and also prejudiced against certain high-risk groups such as the overweight, smokers, and older people.\(^25\) Some method of formal CHD risk assessment is clearly essential for rational prescribing of statins.

Some guidelines use thresholds of total or LDL-cholesterol along with simple counting of risk factors,\(^3,6\) and indeed this policy is still advocated in the Monthly Index of Medical Specialities (MIMS),\(^26\) a prescribing aid widely used by British doctors. In our study, this method was distinctly less accurate than Framingham-based methods that count and weight risk factors for CHD. It failed to treat patients with high and even extremely high CHD risk, while identifying for treatment many with a CHD event risk below 0.6% per year, the present limit of outcome trial evidence for statins.\(^16\) Low accuracy was reported in previous studies,\(^23,27\) and accuracy declines with increasing age beyond 35 years in men and 55 years in women.\(^27\) Use of LDL-cholesterol or total cholesterol thresholds plus risk factor counting identifies a high proportion of the adult population for statin treatment,\(^3,28,29\) for example more than 20% of those aged over 45 years in the US.\(^29\) Many of those identified will have very low CHD risk, and many at high CHD risk will not be treated. Methods of lipid thresholds plus counting of risk factors continue to be used because it is thought that doctors may not understand newer methods of formal CHD risk estimation.\(^30\) That is not our experience. Provided the method of formal CHD risk assessment is simple, it is easier to classify patients by only two numbers, cholesterol and CHD event risk, than to juggle several categorical variables. Methods that use lipid thresholds plus counting of risk factors are unacceptably inaccurate for clinical practice.

A recent comparison of three risk-assessment methods (NCEP guidelines,\(^6\) Sheffield table using total cholesterol,\(^10\) and European guidelines\(^5\)) was carried out in a series of 570 patients without clinical evidence of atherosclerosis referred to a lipid clinic.\(^28\) This showed that the different methods varied markedly in their assessment of CHD risk. However one of the methods tested\(^10\) was not used correctly, and in addition, specificity was entirely ignored. The present study confirms the high sensitivity of the Joint European Task Force chart, but shows that it has very low specificity.

The comparison of Framingham-based methods against CHD risk calculated by PROCAM shows that the Framingham function has external validity, adding to a large body of evidence that it predicts CHD risk accurately in British and northern European populations despite secular changes in CHD incidence.\(^31\) The simple Framingham-based methods are
all capable of detecting most high-risk individuals for treatment, but incorporation of HDL-cholesterol, as the total: HDL cholesterol ratio, greatly enhances the accuracy of risk prediction with either the PROCAM or Framingham risk function as the gold standard. The Framingham function appears robust to many simplifications or approximations, for example omitting left ventricular hypertrophy or categorizing blood pressure, but not to omission of HDL-cholesterol concentration. British doctors may be relatively unfamiliar with the total: HDL cholesterol ratio, and many laboratories do not measure or report this parameter routinely, but the accuracy of CHD risk prediction and statin prescribing would be greatly enhanced by its use. LDL-cholesterol is favoured in the US and by some specialists in Britain and Europe because it is the proximate cause of CHD. However, use of LDL-cholesterol rather than total cholesterol does not improve risk prediction by the Framingham function, and therefore offers no advantage.

Any of the Framingham-based methods studied will improve the prescribing accuracy of doctors who are unable or unwilling to use the full Framingham risk function. The New Zealand chart estimates cardiovascular risk rather than CHD risk, a fact not widely appreciated in practice or even by experts. Despite this, it estimates CHD risk accurately, because cardiovascular risk and CHD risk correlate highly in the Framingham function, but with a ratio of approximately 4:3. Use of the New Zealand chart at a threshold of 2.0% per year in this study actually targets a CHD event rate of about 1.5% per year. The Sheffield tables are designed to assess CHD risk after control of any hypertension, because antihypertensive treatment is currently more cost-effective than statin treatment. They will be less accurate when hypertension is untreated or uncontrolled, although the Sheffield table using the total: HDL cholesterol ratio had a sensitivity of 89% and specificity of 97% for predicting CHD risk in a large population of diabetics not selected for blood pressure level. The estimates of sensitivity and specificity for the Framingham-based methods in the selected high-risk patients we studied should be generalizable, but the positive and negative predictive values for all these methods need to be examined in much larger and unselected samples of the general population.

There is general consensus that statin treatment should be targeted at absolute CHD risk, and at least in Britain and Europe, a consensus that formal methods of estimating CHD risk should be used. However, the problem of setting a policy remains—what threshold of CHD event risk should be set for primary prevention with statins? In the four guidelines assessed by Unwin et al., the policy was set by consensus alone in three, but this was not so for guidance based on the Sheffield table. This was developed after the implications of statin treatment at different levels of CHD risk had been set out explicitly for examination and debate, an important fact that has been overlooked entirely by some. Statin prescribing in Britain is not constrained by benefit to the individual (NNT) or even primarily by cost-effectiveness. The main constraint by far is the high proportion of the adult population likely to need statin treatment and, stemming from this, the very high total cost of treatment and the resource implications for primary care. Complete implementation of statin treatment for secondary prevention plus primary prevention at a CHD event rate ≥3% will entail treating about 8% of all adults, and some believe that even this is not feasible. This policy still seems appropriate for the UK, but treatment at lower CHD risk levels may be appropriate in the future, and at present for other populations with a lower prevalence of CHD risk factors or CHD risk. The SMAC guidance was based on a Sheffield table using total cholesterol alone and cholesterol threshold ≥5.5 mmol/l, which actually extrapolated beyond the evidence available then for primary prevention. High specificity at the expense of sensitivity (Figure 2) was appropriate at that time, but is now too conservative in light of new evidence on primary prevention. The total cholesterol threshold for treatment should be lowered to ≥5.0 mmol/l, and a method with high sensitivity for CHD risk prediction is required, at the expense of specificity if necessary. Methods based on the total: HDL cholesterol ratio (Figure 2) should be preferred.

References


27. Avins AL, Browner WS. Improving the prediction of coronary heart disease to aid in the management of high cholesterol levels. What a difference a decade makes. JAMA 1998; 279:445–9.


