Calculation of coronary risk in Type II diabetes: another cause for concern

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We read with interest the paper by Stevens et al. [1], in which they described a new equation for calculating coronary heart disease (CHD) risk in patients with Type II diabetes mellitus. The new equation, which is based on the U.K. Prospective Diabetes Study (UKPDS) [2], utilizes HbA\(_1c\) as a continuous variable unlike the Framingham risk equations [3], which are only interested in the presence or absence of diabetes. The inclusion of HbA\(_1c\) as a continuous risk factor for CHD in Type II diabetes resulted in a significant increase in the 10-year risk.

The National Service Framework for CHD prevention proposed that statins should be limited to patients with a

![Graph](image)

**Figure 1** Comparison of the direct HDL cholesterol measurement method, marketed by Roche (Y) with the conventional precipitation method (X) using the method of Passing and Bablock for linear regression analysis.

The dashed lines indicate the 95% confidence limit. Similar results were obtained for methods marketed by the companies Sigma, Wako and Randox. (a) Patients with Type I diabetes, and (b) patients with Type II diabetes.

**Key words:** coronary heart disease risk, diabetes mellitus, HDL cholesterol, risk estimation.

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Table 1  Effect of measuring HDL cholesterol by the new methods on the 10-year CHD risk

<table>
<thead>
<tr>
<th>Total cholesterol</th>
<th>HDL-C (mmol/l)</th>
<th>10-year CHD risk %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Direct method</td>
<td>Precipitation method</td>
</tr>
<tr>
<td>5</td>
<td>1.42</td>
<td>1.2</td>
</tr>
<tr>
<td>4.6</td>
<td>1.224</td>
<td>1.0</td>
</tr>
<tr>
<td>6.8</td>
<td>1.026</td>
<td>0.8</td>
</tr>
<tr>
<td>5.2</td>
<td>0.828</td>
<td>0.6</td>
</tr>
</tbody>
</table>

10-year CHD risk of ≥30%, but the Joint British Guidelines for CHD prevention [4] recommended a staged progressive approach to extend drug therapy to patients with a 10-year risk of ≥15%.

The UKPDS equation is capable of identifying more patients above the cut-off level of 30% risk, but probably on average performs similarly to the Framingham risk equations when a cut-off level of ≥15% is used [5].

We would like to highlight another cause for bias in calculating CHD risk in Type II diabetes, that is the value of high-density lipoprotein (HDL) cholesterol. HDL cholesterol is one of the risk factors included in risk calculation by both the UKPDS and the Framingham methods. Until recently, the common method for measuring HDL cholesterol was an indirect two-step procedure. This method involved the addition of divalent cations and polyanions for the precipitation of apoB-containing particles [very-low-density lipoprotein (VLDL) and low-density lipoprotein (LDL)], with subsequent cholesterol determination in the supernatant. These methods agree very well with the reference method, which depends on preparative ultracentrifugation [6]. However, these methods were laborious, using expensive staff time and are not amenable to automation, due to the need for centrifugation.

Several methods have now been introduced for the direct measurement of HDL cholesterol that is readily adaptable to automation procedures. The new methods are also called the homogeneous methods because all the reactions take place in one medium, without the need for separation by centrifugation. The homogeneous methods rely on masking or inactivating the VLDL and LDL, leaving only the HDL cholesterol available to react with cholesterol-measuring reagents. It is possible to automate these methods and make it easy to measure large numbers of HDL cholesterol levels cheaply. They have already replaced the conventional precipitation methods in most clinical laboratories.

We compared the performance of four homogeneous methods with the conventional precipitation method in groups of patients with Type I or Type II diabetes (30 in each group). The four methods are named in this study after the companies which market them as the Wako, Sigma, Roche and Randox.

The new homogeneous methods showed positive bias for patients with diabetes (Figure 1). However, in patients with Type I diabetes, the bias is small and the new homogeneous methods could probably be used safely. The bias in Type II patients is greater and becomes worse at low HDL cholesterol concentrations (<0.9 mmol/l).

Table 1 demonstrates the effect of such bias on the 10-year CHD risk calculated using the computer program recommended by the Joint British Guidelines for CHD prevention. It is evident from the Table that using the homogeneous HDL cholesterol methods is likely to lead to underestimation of the calculated CHD risk and may influence the decision for initiating lipid-lowering therapy in patients with Type II diabetes.

The homogeneous methods are here to stay because of their advantages. We propose that the value of HDL cholesterol measured by a homogeneous method be corrected to remove the positive bias before the value is used to calculate CHD risk. This could be done by incorporating the regression equation into risk calculators used for patients with Type II diabetes.

REFERENCES


Calculation of coronary risk in Type II diabetes: another cause for concern: authors’ reply

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We appreciate the comments by Saeed et al. and agree that the UKPDS Risk Engine, compared with the Framingham equations [1], is likely to identify a greater risk for CHD and stroke for most patients with Type II diabetes. We believe the UKPDS Risk Engine will more accurately predict CHD and stroke risk given that the UKPDS aimed to recruit typical U.K. patients presenting with newly-diagnosed Type II diabetes. [2] The UKPDS Risk Engine takes into account the initial enhanced survival seen in study populations [3].

We agree that all risk calculators require that a standardized approach be used for measuring the included risk factors and that HDL cholesterol determinations are no exception. The UKPDS used an indirect HDL cholesterol method [4] aligned to the U.K. Centre for Disease Control (CDC) reference laboratory. The UKPDS Risk Engine should perform satisfactorily whenever CDC aligned HDL cholesterol measurements are used, but adjustment will be needed for any methods, direct or indirect, that have a significant bias compared with the CDC reference method. The alternative approach suggested, whereby risk calculators could incorporate regression equations that would adjust for all different assay methodologies and laboratory implementations, is impractical.

We were interested by the authors’ suggestion that the bias for the Roche HDL cholesterol method, compared with the conventional precipitation method, may be greater in Type II than in Type I diabetes, but note that that the Figures they provide do not suggest a statistically significant difference.

REFERENCES