Non-HDL Cholesterol Is Less Informative Than the Total-to-HDL Cholesterol Ratio in Predicting Cardiovascular Risk in Type 2 Diabetes

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It has been suggested by some authors that non-HDL cholesterol, defined as total cholesterol minus HDL cholesterol, may be a particularly useful predictor of cardiovascular risk (1) and easier to calculate than the commonly used total-to-HDL cholesterol ratio. We have examined whether the U.K. Prospective Diabetes Study (UKPDS) Risk Engine (2), a coronary heart disease (CHD) risk calculator developed specifically for type 2 diabetes that uses the total-to-HDL cholesterol ratio, could be improved by substituting non-HDL cholesterol.

RESEARCH DESIGN AND METHODS

— The UKPDS Risk Engine encapsulates a parametric model to estimate the risk of CHD, defined as myocardial infarction or sudden cardiac death, derived from the UKPDS, with 53,000 patient-years of follow-up data (3). For this analysis, 4,540 of the 5,102 UKPDS patients were included, for whom sufficient data were available and whose characteristics have been previously reported (2). Briefly, the UKPDS recruited patients with newly diagnosed type 2 diabetes but no recent myocardial infarction or stroke. They were mean age 53 years (range 25–65), 58% male, 83% white-Caucasian, 10% Indian-Asian, 8% Afro-Caribbean, and 30% were smokers at study entry. Mean (±SD) HbA_{1c}, 1–2 years after study entry, was 6.7 ± 1.4%, systolic blood pressure was 136 ± 20 mmHg, total cholesterol was 5.4 ± 1.0 mmol/l, and HDL cholesterol was 1.1 ± 0.25 mmol/l. The UKPDS Risk Engine equation (2) includes the total-to-HDL cholesterol ratio and adjusts for age, duration of diabetes, sex, smoking, ethnic group, HbA_{1c}, and systolic blood pressure.

A new risk equation was constructed that uses non-HDL cholesterol instead of the total-to-HDL cholesterol ratio but otherwise adjusts for the same risk factors. Equations were fitted by maximum likelihood methods. To compare model fit to the original data, we used Akaike's Information Criterion (AIC) defined by $2 \times (-\log \text{likelihood} + \text{number of parameters})$, in which lower values of AIC correspond to better risk prediction (4). We used likelihood-ratio tests to compare both models with a reference model that included both total and HDL cholesterol, adjusting for the same risk factors.

Receiver-operating characteristic (ROC) curves were used to assess the sensitivity and specificity of the models in patients entering the UKPDS 5-year poststudy monitoring program. CHD risk was calculated over the duration of poststudy monitoring in 2,885 patients with data available and without prior CHD at entry to poststudy monitoring. Area under the ROC curve (aROC) was calculated for each model, with high aROC indicating a more useful model, and a *P* value was calculated for the difference in aROC between the total-to-HDL cholesterol and non-HDL models (5). The number of patients with a 10-year CHD risk in excess of 15%, as used by some clinical guidelines (6), was also determined.

RESULTS

— A total of 517 CHD events occurred during 29,878 person-years of follow-up. The hazard ratio for total-to-HDL cholesterol ratio was 1.23 per unit, equivalent to 1.36 per SD (95% CI 1.26–1.45). The hazard ratio for non-HDL cholesterol was 1.33 per mmol/l, equivalent to 1.35 per SD (95% CI 1.24–1.47). The hazard ratios for nonlipid risk factors were not significantly different between the total-to-HDL cholesterol model and the non-HDL model. The AIC difference between the models was 11.2, with the total-to-HDL cholesterol ratio equation a stronger predictor (lower AIC) of risk than the non-HDL cholesterol equation. In likelihood-ratio tests the original model was equivalent to a full model containing separate terms for total cholesterol and HDL cholesterol ($P = 0.38$), whereas the non-HDL cholesterol model was significantly worse than the full model ($P < 0.0001$).

In UKPDS poststudy monitoring, 176 CHD events were observed in 2,885 patients. The aROC was 0.678 for the total-to-HDL cholesterol ratio model and 0.666 for the non-HDL cholesterol model ($P = 0.41$). Patients were classified similarly (94%) by both equations (Table 1), with 73.5 and 71.3%, respectively, at >15% CHD risk ($P < 0.0001$).

We verified (data not shown) that a non-HDL-to-HDL cholesterol ratio gives identical results to the total-to-HDL cho-

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Received for publication 17 January 2005 and accepted in revised form 21 March 2005.

Abbreviations: AIC, Akaike's Information Criterion; aROC, area under the ROC curve; CHD, coronary heart disease; ROC, receiver-operating characteristic; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*CHD risk classification of 2,885 patients entering UKPDS poststudy monitoring by two multivariable equations*

	10-year CHD risk by an equation using non-HDL cholesterol	
	≤15%	>15%
10-year CHD risk by an equation using total-to-HDL cholesterol ratio		
≤15%	708	57
>15%	119	2,001

lesterol ratio (note that total-to-HDL cholesterol ratio = 1 + non-HDL-to-HDL cholesterol ratio). The UKPDS Risk Engine model differs from the total-to-HDL cholesterol ratio model used here only in that it log transforms the cholesterol ratio, which further improves model fit (AIC decreased by a further 6.6). The present analysis avoids log transformation because it introduces difficulties with the likelihood-ratio tests. We verified (data not shown) that the AIC and ROC analyses are not materially affected by log transformation.

CONCLUSIONS — Total-to-HDL cholesterol ratio is a stronger predictor of CHD risk than non-HDL cholesterol in this prospective study of a cohort with type 2 diabetes. The similarity of the ROC curves indicates that the difference is not clinically important, at least in type 2 diabetic populations. This confirms previous results in 746 diabetic men (7).

The absolute values of aROC reported here are similar to those for other CHD risk models (7–9) but lower than considered desirable in other fields (10), indicating that primary prevention of CHD is a difficult area for risk modelers. The similarity in aROC between the models confirms the finding from the Atherosclerosis Risk in Communities study that when a model already contains several major CHD risk factors, further refinements have diminishing returns (9).

Although non-HDL cholesterol is an easier measure to calculate without a computer or nomogram, there are theoretical reasons why the total-to-HDL cholesterol ratio is preferable. Consider two hypothetical patients with identical non-HDL cholesterol values of 4.0 mmol/l but one with total cholesterol 5.0 mmol/l and HDL cholesterol 1.0 mmol/l and the other with total cholesterol 5.5 mmol/l and HDL cholesterol 1.5 mmol/l. Their total-to-HDL cholesterol ratios are 5.0 and 3.7, respectively, reflecting the better lipid profile of the second patient, but this distinction is not apparent from the non-HDL cholesterol value alone.

The analyses reported here confirm the statistical advantages of the total-to-HDL cholesterol ratio in large samples but also show that the improvement is unlikely to be important in clinical practice. The UKPDS Risk Engine software uses total cholesterol and HDL cholesterol in the most powerful way to forecast CHD risk.

Acknowledgments — R.J.S. is funded by the Health Foundation. R.L.C. is funded by Diabetes UK.

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