Clinical Usefulness of Different Lipid Measures for Prediction of Coronary Heart Disease in Type 2 Diabetes

A report from the Swedish National Diabetes Register

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OBJECTIVE—We assessed the association between different blood lipid measures and risk of fatal/nonfatal coronary heart disease (CHD).

RESEARCH DESIGN AND METHODS—We conducted an observational study of patients with type 2 diabetes from the Swedish National Diabetes Register. Baseline LDL cholesterol, non-HDL cholesterol, ratio of non-HDL to HDL cholesterol (non-HDL:HDL), and ratio of triacylglycerol to HDL cholesterol (TG:HDL) was measured in 18,673 patients aged 30–70 years, followed for a mean of 4.8 years from 2003 to 2007.

RESULTS—Hazard ratios (HRs) for CHD per 1-SD increment in lipid measures were 1.23 with non-HDL:HDL, 1.20 with non-HDL cholesterol, 1.17 with LDL cholesterol, and 1.15 with TG:HDL (all $P < 0.001$ when adjusted for clinical characteristics and nonlipid risk factors). The best global model fit was found with non-HDL:HDL. When patients within the lowest tertile of a lipid measure were compared with those with all lipid measures within the highest tertile, the adjusted HR for CHD was 0.62 with non-HDL:HDL <3.5 mmol/L, 0.65 with non-HDL cholesterol <3.3 mmol/L, and 0.70 with LDL cholesterol <2.5 mmol/L (all $P < 0.001$). The lowest tertile of LDL and non-HDL cholesterol corresponded with treatment targets according to U.S. and European guidelines. HRs for CHD were 0.52, 0.62, and 0.66 with the lowest deciles of non-HDL:HDL, non-HDL cholesterol, and LDL cholesterol ≤1.8 mmol/L (all $P < 0.001$). Mean TG:HDL was considerably lower in patients within the lowest tertile of non-HDL:HDL, 0.82 ± 0.47, than in those within the lowest tertile of LDL cholesterol (<2.5 mmol/L), 1.49 ± 1.03.

CONCLUSIONS—Non-HDL:HDL had a stronger effect on CHD risk than LDL cholesterol, and low TG:HDL values were more often seen within the lowest non-HDL:HDL tertile than within the lowest LDL cholesterol tertile. LDL cholesterol was not the best predictor of CHD risk in type 2 diabetes.

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Randomized controlled clinical trials have established the clinical benefits of lowering LDL cholesterol levels for risk reduction of coronary heart disease (CHD) (1). The National Cholesterol Education Program Adult Treatment Panel (ATP) III (2) and the American Diabetes Association (3) have recommended LDL cholesterol <2.5 mmol/L as the primary treatment goal in patients with diabetes and hyperlipidemia.

ATP III has also identified non-HDL cholesterol (the sum of LDL and VLDL) <3.3 mmol/L as a secondary treatment target in patients with triacylglycerol >2.3 mmol/L or HDL cholesterol <1.0 mmol/L (2). European guidelines recommend the same targets for LDL and non-HDL cholesterol (4,5), and these as well as those of the U.S. National Cholesterol Education Program (1) and the American Diabetes Association (3) have also recently underlined LDL cholesterol ≤1.8 mmol/L as an optional goal for patients with diabetes and overt cardiovascular disease (CVD).

Against this background, we assessed the clinical usefulness of several lipid measures with regard to the risk of CHD in an observational study of 18,673 patients with type 2 diabetes in the Swedish National Diabetes Register (NDR). The main aim was to evaluate LDL cholesterol as a risk factor in comparison with the ratio of non-HDL cholesterol to HDL cholesterol (non-HDL:HDL).

RESEARCH DESIGN AND METHODS

Swedish NDR

The Swedish NDR was initiated in 1996 as a tool for local quality assurance in diabetes care. Annual reporting to the NDR is carried out by trained physicians and nurses via the Internet or clinical records databases during patient visits at hospitals and primary health care centers nationwide. All included patients have agreed by informed consent to register before inclusion. The regional ethics review board at the University of Gothenburg approved this study. Several reports concerning risk factor control and risk prediction in the NDR have previously been published (6–10).

Subjects

This observational study included 18,673 patients with type 2 diabetes aged 30–70 years, 13% of whom had a history of CVD, and with data available for all

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analyzed variables followed prospectively for 5 years from 2003 to 2007. The definition of type 2 diabetes was treatment with diet only, oral hypoglycemic agents only, or onset age of diabetes ≥40 years and insulin only or combined with oral agents. Only 1% had onset age <30 years, and 3% had onset age <40 years.

Examination at baseline

Clinical characteristics at baseline in 2002–2003 were as follows: age, sex, diabetes duration, type of hypoglycemic treatment, total cholesterol, HDL cholesterol, triacylglycerol, HbA_{1c}, weight, height, smoking, systolic blood pressure, use of lipid-lowering drugs, and cumulative microalbuminuria. BMI (measured in kilograms per meters squared) was calculated as weight divided by the square of height in meters. The Swedish standard for blood pressure recording, used in the NDR, is the mean of two readings (Korotkoff 1–5) with a cuff of appropriate size after at least 5 min of rest. A smoker was defined as a patient smoking one or more cigarettes/day, smoking tobacco using a pipe, or stopped smoking within the past 3 months.

Laboratory analyses of HbA_{1c} and serum lipids were carried out at local laboratories. HbA_{1c} analyses are quality assured nationwide by regular calibration with the high-performance liquid chromatography Mono-S method. HbA_{1c} values were converted to the Diabetes Control and Complications Trial standard values using the following formula: HbA_{1c} (DCCT) = 0.923 × HbA_{1c} (Mono-S) + 1.345; R^2 = 0.998 (11). LDL cholesterol values were calculated using Friedewald formula if triacylglycerol levels were <4.0 mmol/L (12). Albuminuria was defined as cumulative microalbuminuria: urine albumin excretion >20 μg/min in two of three consecutive tests.

Follow-up and definition of end points

All patients were followed from the baseline examination until a first CHD event, death, or censor date 31 December 2007. Mean follow-up was 4.8 years. Nonfatal or fatal CHD was used as the end point in this study. Nonfatal CHD was defined as nonfatal myocardial infarction (ICD-10 code I21), unstable angina (ICD-10 code I20.0), percutaneous coronary intervention or coronary artery bypass grafting, and fatal CHD defined as ICD-10 codes I20–I25. A history of CVD was the composite of CHD and/or stroke (nonfatal/fatal cerebral infarction, intracerebral hemorrhage, or unspecified stroke: ICD-10 codes I61, I63, I64, and I67.9).

All events were retrieved by data linkage with the Swedish Cause of Death and Hospital Discharge Registers, which is a reliable validated alternative to revised hospital discharge and death certificates (13,14). In total, 1,156 fatal/nonfatal CHD events occurred based on 79,342 person-years.

Statistical methods

Baseline characteristics are presented as means ± 1 SD, median (25th−75th percentile), or frequencies in Table 1. Spearman correlation coefficients were estimated between different lipid measures.

Cox regression analysis was used to estimate hazard ratios (HRs) (95% CIs) for risk of CHD per 1-SD increase in baseline lipid measures used as continuous variables (Table 2), adjusted for covariates as given in Table 2. The proportional hazards assumption was confirmed for all covariates with the Kolmogorov-type supremum test using resampling and with the test of all time-dependent covariates simultaneously introduced. Interactions between lipid measures and covariates were analyzed with maximum-likelihood estimation and were found to be nonsignificant for all included covariates. Updated mean values of blood lipids were also calculated, treated as strictly time dependent, from baseline to a year before an event or, otherwise, to censor date, with the last observation carried forward for missing data.

All patients were divided in quartiles of lipid measures, and adjusted HRs for CHD were estimated with higher quartiles of each lipid measure and with quartile 1 as the reference (Table 3). Adjusted HRs for CHD were also estimated using patients with all lipid measures in the highest tertile, tertile 3, as the reference, compared with tertile 1 or decile 1 of each lipid measure (Table 3). A Cox proportional hazards regression model was used to estimate adjusted 5-year event rates (1 − survival rate) of CHD, related to different lipid measures across their ranges (Fig. 1) and adjusted for covariates as given in Table 2.

Table 1—*Baseline characteristics in 18,673 type 2 diabetic patients aged 30–70 years*

	All patients
Lipid measures	
Total cholesterol (mmol/L)	5.06 ± 0.99/5.0 (4.4–5.7)
Non-HDL cholesterol (mmol/L)	3.75 ± 0.98/3.7 (3.1–4.4)
LDL cholesterol (mmol/L)	2.99 ± 0.90/2.9 (2.4–3.5)
HDL cholesterol (mmol/L)	1.31 ± 0.41/1.2 (1.0–1.5)
Triacylglycerol (mmol/L)	1.70 ± 0.77/1.6 (1.1–2.2)
TC:HDL	4.16 ± 1.26/4.0 (3.3–4.9)
Non-HDL:HDL	3.16 ± 1.26/3.0 (2.3–3.9)
LDL:HDL	2.49 ± 1.01/2.4 (1.8–3.1)
TG:HDL	1.48 ± 0.92/1.3 (0.8–2.0)
Clinical features	
Age (years)	60 ± 8
Diabetes duration (years)	7 ± 6
HbA_{1c} (%)	7.3 ± 1.2
Systolic blood pressure (mmHg)	140 ± 17
BMI (kg/m^2)	29.6 ± 5.2
Male sex	60.4
Smoking	18.9
Albuminuria >20 μg/min	19.8
History of cardiovascular disease	13.2
Treatment	
Lipid-lowering drugs	42.0
Hypoglycemic treatment	
Diet only	22.9
Oral agents only	38.4
Oral agents and insulin	17.7
Insulin only	21.0

Data are means ± SD/median (25th–75th percentile), means ± SD, or %. SI conversion factor: to convert blood lipids from millimoles per liter to milligrams per deciliter, divide by 0.026 and by 0.011 for triacylglycerol.

Table 2—*HRs for baseline and updated mean values of different lipid measures and fatal/nonfatal CHD at Cox proportional hazards regression, with calibration, discrimination, and model fit, in 18,673 type 2 diabetic patients followed for 5 years with 1,156 CHD events*

	Baseline values					Updated mean values	
	Incidence		Calibration: ratio of	Discrimination:	Goodness of fit:	Incidence	
Lipid measures	HR (95% CI)*	Wald χ^2	O to P rates	*C* statistic	LR χ^2/AIC	HR (95% CI)*	Wald χ^2
Ratios							
TC:HDL	1.23 (1.17–1.30)	55†	7.09:7.09	0.70	564/21,927	1.38 (1.32–1.46)	158†
Non-HDL:HDL	1.23 (1.17–1.30)	55†	7.09:7.09	0.70	564/21,927	1.38 (1.32–1.46)	158†
LDL:HDL	1.22 (1.15–1.28)	50†	7.09:7.08	0.70	559/21,931	1.37 (1.30–1.44)	154†
Single measures							
Non-HDL	1.20 (1.14–1.27)	40†	7.09:7.09	0.70	551/21,939	1.38 (1.32–1.46)	144†
LDL cholesterol	1.17 (1.10–1.24)	28†	7.09:7.09	0.70	540/21,951	1.33 (1.26–1.41)	107†
TG:HDL	1.15 (1.08–1.21)	23†	7.09:7.11	0.70	534/21,956	1.20 (1.14–1.26)	49†
HDL cholesterol	0.85 (0.79–0.91)	20†	7.09:7.11	0.70	534/21,956	0.79 (0.73–0.85)	41†
Total cholesterol	1.14 (1.08–1.21)	20†	7.09:7.10	0.70	533/21,958	1.29 (1.22–1.37)	82†
Triacylglycerol	1.13 (1.06–1.19)	16†	7.09:7.11	0.70	528/21,963	1.17 (1.10–1.23)	31†
Combinations							
LDL cholesterol	1.17 (1.10–1.24)	29†	7.09:7.10	0.70	563/21,930	1.33 (1.26–1.41)	113†
TG:HDL	1.15 (1.09–1.22)	24†				1.21 (1.15–1.27)	56†

Wald χ^2 statistic: a higher value indicates stronger association. *C* statistic: a higher value indicates a better discrimination. Likelihood ratio (LR) χ^2 statistics from the Cox model: a higher value indicates a better global fit. AIC from the Cox model: a lower value indicates a better trade-off between the likelihood of a model against its complexity. Ratio of O to P rates, ratio of observed 5-year Kaplan-Meier CHD rate (%) to predicted mean rate (%) in a Cox proportional hazards model. *HR (95% CI) for a 1-SD increase in a lipid measure at Cox regression, with adjustment for age, sex, diabetes duration, type of hypoglycemic treatment, HbA_{1c}, systolic blood pressure, smoking, BMI, albuminuria >20 μg/min, and a history of CVD. †$P < 0.001$.

All statistical analyses were performed with SAS (version 9.1.3; SAS Institute, Cary, NC). A P value < 0.05 at two-tailed test was considered statistically significant.

RESULTS—Table 1 gives baseline characteristics in all 18,673 participants. Mean age and mean diabetes duration were 60 and 7 years, respectively, and 60% of the patients were men.

Correlations

Values of non-HDL:HDL were always one unit lower than values of the ratio of total cholesterol to HDL cholesterol (TC:HDL). The Spearman correlation coefficient was 0.72 between non-HDL:HDL and the ratio of triacylglycerol to HDL cholesterol (TG:HDL), 0.37 between non-HDL cholesterol and TG:HDL, and only 0.05 between LDL cholesterol and TG:HDL.

HRs for baseline lipids

In all patients, a high HR of 1.23 was found for fatal/nonfatal CHD per 1-SD increase in baseline non-HDL:HDL after adjustment for clinical characteristics and nonlipid risk factors, with the best global model fit according to the highest likelihood ratio χ^2 and the lowest Akaike information criterion (AIC). Calibration of this model was good with a ratio of observed to predicted rates of 1.0. Area under the receiver operating characteristic curve as given by the *C* statistic for discrimination was 0.70 (Table 2).

Adjusted HRs per 1-SD increase in the ratio of LDL cholesterol to HDL cholesterol and in non-HDL cholesterol were 1.22 and 1.20, respectively, with lower χ^2 and higher AIC. A lower HR of 1.17 was found for LDL cholesterol, with still lower χ^2 and higher AIC.

In agreement with the low correlation between LDL cholesterol and TG:HDL, the use of these two predictors simultaneously showed unchanged HRs for CHD compared with the use of each of them separately (Table 2). The sum of their Wald χ^2 and their combined global likelihood ratio χ^2 and AIC were almost the same as for non-HDL:HDL.

Analysis of 16,203 patients with no previous CVD showed a similar picture; adjusted HR was 1.27 (95% CI 1.19–1.35; $P < 0.001$) for non-HDL:HDL and lower for LDL cholesterol (1.21 [1.13–1.29; $P < 0.001$]).

A similar picture was also seen in two smaller subgroups of patients with or without lipid-lowering drugs, though more obviously in patients without lipid-lowering drugs, who also exhibited higher mean values of non-HDL:HDL, non-HDL cholesterol, and LDL cholesterol (Supplementary Tables 1–2).

HRs for updated mean lipids

A similar picture was also seen for updated mean values of the lipid measures in all patients (Table 2). A high adjusted HR of 1.38 was found for fatal/nonfatal CHD per 1-SD increase in updated mean non-HDL:HDL, whereas the adjusted HR for updated mean LDL cholesterol was lower (1.33).

Splines of CHD and lipid measures

Figure 1 shows splines of 5-year rates with 95% CIs of fatal/nonfatal CHD as a cubic function of four lipid measures across their ranges in a Cox proportional hazards regression model in all patients. The increase in CHD rate was small at lower levels of LDL cholesterol but increased more rapidly at higher values (>4 mmol/L) (Fig. 1*A*). Both non-HDL:HDL and TG:HDL demonstrated much greater and almost linear increases in CHD rates across their ranges (Fig. 1*C* and *D*).

Patients with higher or lower lipid values

All patients were categorized in quartiles of a lipid measure, from the highest quartile 4 to the lowest quartile 1 as reference. HR for

Table 3—*HRs for fatal/nonfatal CHD and quartiles or tertiles of lipid measures at Cox proportional hazards regression in 18,673 patients with type 2 diabetes followed for 5 years*

Lipid measures	HR (95% CI)*	*P*
Quartiles		
Non-HDL:HDL		
Quartile 1 (<2.27)	1.0	
Quartile 2 (2.27–2.99)	1.31 (1.08–1.58)	0.007
Quartile 3 (3.0–3.90)	1.71 (1.42–2.05)	<0.001
Quartile 4 (≥3.91)	1.94 (1.61–2.32)	<0.001
Non-HDL cholesterol (mmol/L)		
Quartile 1 (<3.10)	1.0	
Quartile 2 (3.10–3.69)	1.20 (1.01–1.43)	0.04
Quartile 3 (3.70–4.34)	1.37 (1.16–1.63)	<0.001
Quartile 4 (≥4.35)	1.72 (1.46–2.03)	<0.001
LDL cholesterol (mmol/L)		
Quartile 1 (<2.36)	1.0	
Quartile 2 (2.36–2.92)	1.12 (0.94–1.32)	0.2
Quartile 3 (2.93–3.53)	1.14 (0.97–1.35)	0.1
Quartile 4 (≥3.54)	1.51 (1.28–1.78)	<0.001
TG:HDL		
Quartile 1 (<0.80)	1.0	
Quartile 2 (0.80–1.26)	1.34 (1.11–1.61)	0.003
Quartile 3 (1.27–1.95)	1.54 (1.28–1.85)	<0.001
Quartile 4 (≥1.96)	1.61 (1.34–1.95)	<0.001
Tertiles		
Non-HDL:HDL		
Tertile 3 (ref.)†	1.0	
Tertile 1 (<2.5)	0.62 (0.50–0.77)	<0.001
Decile 1 (<1.7)	0.52 (0.38–0.71)	<0.001
Non-HDL cholesterol (mmol/L)		
Tertile 3 (ref.)†	1.0	
Tertile 1 (<3.3)	0.65 (0.53–0.80)	<0.001
Decile 1 (<2.6)	0.62 (0.47–0.81)	<0.001
LDL cholesterol (mmol/L)		
Tertile 3 (ref.)†	1.0	
Tertile 1 (2.5)	0.70 (0.58–0.85)	<0.001
Decile 1 (≤1.8)	0.66 (0.51–0.86)	<0.001
TG:HDL		
Tertile 3 (ref.)†	1.0	
Tertile 1 (<0.9)	0.66 (0.53–0.82)	<0.001
Decile 1 (<0.5)	0.55 (0.39–0.78)	<0.001

*HRs adjusted for age, sex, diabetes duration, type of hypoglycemic treatment, HbA_{1c}, systolic blood pressure, smoking, BMI, albuminuria >20 μg/min, and a history of CVD. †Reference group: tertile 3 of non-HDL:HDL (≥3.6), non-HDL cholesterol (≥4.1 mmol/L), LDL cholesterol (≥3.3 mmol/L), and TG:HDL (≥1.7). Tertile 1 and decile 1 of a lipid measure were compared with this reference group.

CHD with quartile 4 versus quartile 1 was highest for non-HDL:HDL (1.94), lower for non-HDL cholesterol and TG:HDL, and considerably lower for LDL cholesterol (1.51) (all $P < 0.001$) (Table 3).

Patients were also categorized for a comparison between tertile 1 of a specific lipid measure versus the highest tertile 3 of all analyzed lipid measures as reference to enable a comparison between low levels of lipid measures at their treatment targets (Table 3). HR for tertile 1 of non-HDL:HDL, 0.62, was noticeably lower for tertile 1 of LDL cholesterol <2.5 mmol/L, 0.70. Similarly, when decile 1 (the lowest decile) of a lipid measure was compared with this reference group, HR for decile 1 of non-HDL:HDL, 0.52, was noticeably lower than that for tertile 1 of LDL cholesterol ≤1.8 mmol/L, 0.66.

Triacylglycerol and HDL cholesterol by subgroups

Patients with tertile 1 of non-HDL:HDL had a mean TG:HDL of 0.82 ± 0.5, lower than with tertile 1 of LDL:HDL or non-HDL cholesterol and considerably lower than with tertile 1 of LDL cholesterol, 1.49 ± 1.0 (Supplementary Table 3). Similarly, mean triacylglycerol was considerably higher and mean HDL cholesterol lower with tertile 1 of non-HDL:HDL than with tertile 1 of LDL cholesterol.

CONCLUSIONS—This observational study of 18,673 unselected patients with type 2 diabetes in clinical practice followed for 5 years challenges the current role of LDL cholesterol as the most important blood lipid marker of CHD risk. We compared the lipid ratio non-HDL:HDL (including non-HDL cholesterol and excluding LDL cholesterol) with LDL cholesterol, which is the key blood lipid risk factor in present treatment guidelines. Our study demonstrates that non-HDL:HDL, always one unit lower than TC:HDL (as previously reported [15]), can efficiently evaluate the ratio of the sum of atherogenic LDL cholesterol and VLDL lipoproteins represented by non-HDL cholesterol to the potentially cardioprotective HDL cholesterol. We show that adjusted HR for fatal/nonfatal CHD was higher with non-HDL:HDL than with the single measure LDL cholesterol per 1-SD increment across the range. A reason for the weaker association between LDL cholesterol and CHD may be that LDL cholesterol values do not entirely reflect the role of small dense and atherogenic LDL cholesterol particles (16,17).

Similar findings of a higher effect of non-HDL:HDL than LDL cholesterol on risk of fatal/nonfatal CVD have recently been reported in three previous observational studies. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study of 9,795 patients with type 2 diabetes (mean age 63 years), patients were followed for a median of 5 years (18). HRs for CVD, adjusted for nonlipid risk factors, were higher with non-HDL:HDL per 1-SD increment across the range than with LDL cholesterol (1.28 vs. 1.16, respectively, in fenofibrate-treated and 1.21 vs. 1.05 in placebo-administered patients). The UK Prospective Diabetes Study (UKPDS) also found non-HDL:HDL to be better than non-HDL cholesterol as predictor of CHD in type 2 diabetes (15). A report from Framingham on 3,322 middle-aged nondiabetic subjects with a median follow-up of 15 years also described a higher adjusted HR for fatal/nonfatal CHD with TC:HDL than with LDL cholesterol per 1-SD increment

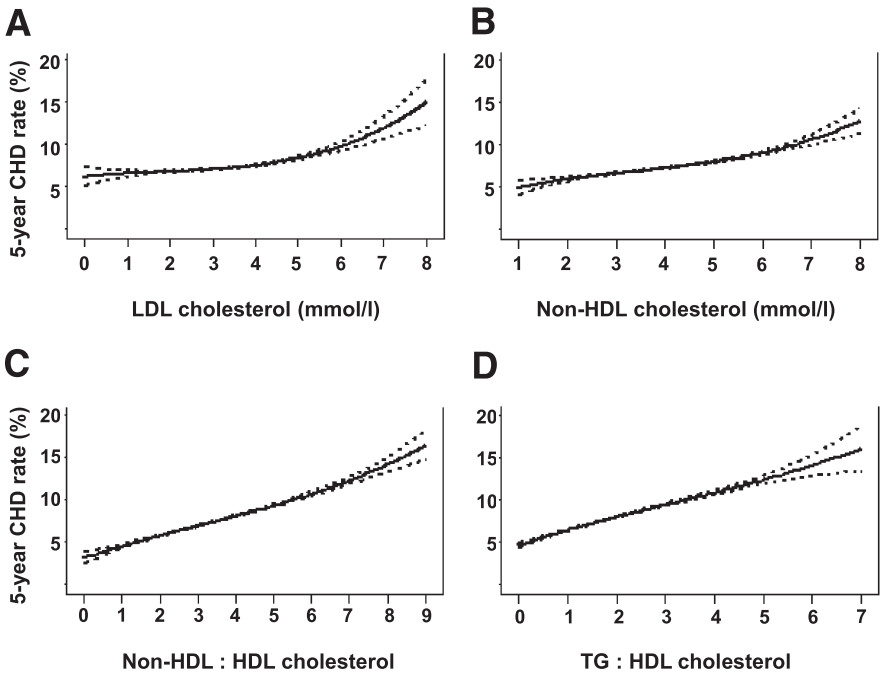

Figure 1—*Five-year rates of CHD by lipid measures per one-unit increase in a Cox proportional hazards model of 18,673 patients. In each figure, the spline represents event rates (solid line) with 95% CIs (dashed lines) of fatal/nonfatal CHD as a cubic function of the lipid measure.*

(1.39 vs. 1.11–1.20, respectively, in men and women [19]). As in our study, global model fit was improved with TC:HDL compared with non-HDL cholesterol and LDL cholesterol. Calibration, according to the ratio of observed to predicted rates, was good with all lipid measures in our study, and the *C* statistic for discrimination was generally 0.70.

Both the FIELD (18) and the Framingham (19) studies also conclude that TC:HDL, non-HDL:HDL, and LDL:HDL as traditional lipid ratios were as strong as the ratio of apolipoprotein (apo)B to apoA-1 in predicting risk, which does not support measurement of apoB or apoA-I in clinical practice when nonfasting total cholesterol, non-HDL cholesterol, and HDL cholesterol measurements are available. Furthermore, a comparison of the highest versus the lowest quartile of a lipid measure in our study showed that the highest adjusted HR for CHD was found with non-HDL:HDL—higher than for LDL cholesterol (Table 3). Similar findings were also reported in the FIELD study (18).

This study also focused on a comparison of the effect of low levels at treatment targets of lipid measures on CHD risk, which was not previously presented in the FIELD, UKPDS, or Framingham studies. When HR for CHD with the lowest tertile 1 of a lipid measure was compared with the highest tertile 3 of all lipid measures, the lowest adjusted HR was found with non-HDL:HDL (0.62), with a considerably higher HR for LDL cholesterol (0.70). Tertile 1 of LDL cholesterol (<2.5 mmol/L) corresponded with the recommended treatment goal according to ATP III and European guidelines (2–5). A similar picture was also seen regarding the lowest decile 1 of non-HDL:HDL compared with decile 1 of LDL cholesterol, and this comparison was included because decile 1 of LDL cholesterol (≤1.8 mmol/L) corresponded with the recently recommended target for diabetes and overt CVD (3–5). Splines of fatal/nonfatal CHD rates across the range of lipid measures in an adjusted Cox proportional hazards model underlined this finding, also emphasizing the idea of "the lower, the better" at low levels of the lipid measures, especially regarding non-HDL:HDL (Fig. 1). A sharp and almost linear decrease in fatal/nonfatal CHD rate was seen with lower non-HDL:HDL (Fig. 1*C*). In contrast, the event rate decrease was obviously smaller at lower LDL cholesterol values (<4 mmol/L [Fig. 1*A*]). Thus, non-HDL:HDL had a better capacity than LDL cholesterol to predict and differentiate CHD risk at lower target values.

We also analyzed TG:HDL in this study: a variable representing diabetic dyslipidemia and a marker for insulin resistance primarily involving the glycogen synthesis pathway (20). Accumulating evidence to date indicates that insulin resistance significantly contributes to accelerated atherosclerosis and development of CVDs (20–24). Even if HRs for CHD were lower with TG:HDL across the range, the spline with TG:HDL showed a sharp and almost linear decrease in CHD rate with lower TG:HDL values (Fig. 1*D*). The combined use of both TG:HDL and LDL cholesterol as predictors of CHD simultaneously did not change their HRs (Table 2). However, the Wald χ^2 statistic for non-HDL:HDL was almost the same as the sum of Wald χ^2 for TG:HDL and LDL cholesterol, underlining that non-HDL:HDL was as good a predictor of CHD as the combined use of TG:HDL and LDL cholesterol. Finally, when we analyzed mean TG:HDL among patients with the lowest tertile 1 of lipid measures, those with tertile 1 of non-HDL:HDL achieved a considerably lower mean TG:HDL than those with tertile 1 of LDL:HDL, non-HDL, or LDL cholesterol (Supplementary Table 3). This underlines the better capacity of non-HDL:HDL to also achieve improved TG:HDL.

This observational study allowed for an analysis of patients receiving daily treatment at hospital and primary care clinics nationwide during recent years, with no exclusion criteria regarding risk factors, representing a true picture of routine clinical diabetes care. A major strength was the large number of patients and person-years. The capture of data on the outcomes was based on reliable and validated national registers of morbidity and mortality. Unmeasured confounding may exist because of unknown and not included covariates and because of changes in risk factors or treatments. However, substantial adjustments were made for clinical characteristics and nonlipid risk factors, including albuminuria as a marker of microangiopathy. Interactions between lipid measures and all covariates were excluded. Forty-two percent of the patients were treated with lipid-lowering agents at baseline. It is possible that this proportion increased during the course of the follow-up period, and the effect of such changes was evaluated with additional use of updated mean blood lipids (except for baseline values). The use of lipid-lowering treatment in Sweden has recently been addressed in a cross-sectional study during a later study period showing that the mean doses of the statins were only low to moderate (25).

In conclusion, although U.S. and European guidelines emphasize LDL cholesterol as the primary treatment target for CHD risk prediction, with non-HDL cholesterol as a secondary target in patients with elevated TG, this study has demonstrated that non-HDL:HDL, which is easily measured in the nonfasting state, seems better than LDL cholesterol for prediction of CHD risk in patients with type 2 diabetes. Furthermore, this study has also demonstrated a stronger effect of lower non-HDL:HDL values than of LDL cholesterol <2.5 mmol/L and has demonstrated that low TG:HDL values were considerably better achieved in patients with lower non-HDL:HDL values than with LDL cholesterol <2.5 mmol/L. The clinical importance of these findings is underlined by the supposed strong association between TG:HDL and insulin resistance, where insulin resistance as part of the metabolic syndrome should be regarded as an important background risk factor for CHD (20).

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