HDL Cholesterol as a Residual Risk Factor for Vascular Events and All-Cause Mortality in Patients With Type 2 Diabetes

*Shahnam Sharif,[1] Yolanda van der Graaf,[2] Hendrik M. Nathoe,[3] Harold W. de Valk,[4] Frank L.J. Visseren,[1] and Jan Westerink,[1] on behalf of the SMART Study Group**

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OBJECTIVE

To evaluate whether low HDL cholesterol (HDL-c) levels are a risk factor for cardiovascular disease and mortality in patients with type 2 diabetes and whether it remains a residual risk factor when attaining low LDL cholesterol (LDL-c) treatment goals or when LDL-c is treated with intensive lipid-lowering therapy.

RESEARCH DESIGN AND METHODS

We performed a prospective cohort study of 1,829 patients with type 2 diabetes included in the Second Manifestations of ARTerial disease (SMART) cohort. Cox proportional hazard models were used to evaluate the risk of HDL-c on cardiovascular events and all-cause mortality. Analyses were performed in strata of LDL-c levels (<2.0, 2.0–2.5, and >2.5 mmol/L) and lipid-lowering therapy intensity and were adjusted for age, sex, BMI, smoking, alcohol, LDL-c, triglycerides, systolic blood pressure, estimated glomerular filtration rate, glucose, and HbA_{1c}.

RESULTS

A total of 335 new cardiovascular events and 385 deaths occurred during a median follow-up of 7.0 years (interquartile range 3.9–10.4). No relation was found between plasma HDL-c and cardiovascular events (hazard ratio [HR] 0.97, 95% CI 0.93–1.01) or all-cause mortality (HR 0.99, 95% CI 0.96–1.03). Subgroup analysis supported effect modification by plasma LDL-c levels. In patients with LDL-c levels <2.0 mmol/L, higher HDL-c was related to higher risk for all-cause mortality (HR 1.14, 95% CI 1.07–1.21). Higher HDL-c was also related to higher risk for cardiovascular events in patients with LDL-c levels <2.0 mmol/L (HR 1.10, 95% CI 1.07–1.21) in contrast to patients with LDL-c levels between 2.0 and 2.5 mmol/L (HR 0.85, 95% CI 0.75–0.95) and >2.5 mmol/L (HR 0.96, 95% CI 0.91–1.00).

CONCLUSIONS

In high-risk patients with type 2 diabetes with LDL-c levels <2.0 mmol/L, higher HDL-c at baseline is unexpectedly related to a higher risk for cardiovascular events and all-cause mortality in contrast to high-risk patients with type 2 diabetes with LDL-c levels between 2.0 and 2.5 mmol/L.

As a result of aging, urbanization, and associated lifestyle changes, the prevalence of type 2 diabetes is globally increasing (1). In an attempt to lower the high risk for cardiovascular disease in patients with type 2 diabetes, emphasis has been placed on improving glycemic control, lowering blood pressure, and improving the dyslipidemia

[1]Department of Vascular Medicine, University Medical Center Utrecht, Utrecht, the Netherlands
[2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands
[3]Department of Cardiology, University Medical Center Utrecht, Utrecht, the Netherlands
[4]Department of Internal Medicine, University Medical Center Utrecht, Utrecht, the Netherlands

Corresponding author: Jan Westerink, j.westerink-3@umcutrecht.nl.

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characteristic of patients with type 2 diabetes (2). Although the dyslipidemia associated with type 2 diabetes is mainly characterized by high triglycerides (TGs), low HDL cholesterol (HDL-c), and elevated small-dense LDL cholesterol (LDL-c) particles (3), the primary lipid-lowering therapy in patients with type 2 diabetes has been LDL-c lowering by inhibition of hydroxymethylglutaryl-coA reductase with a statin. This approach is mirrored in current cardiovascular prevention guidelines which mainly focus on LDL-c treatment goals or statin therapy in patients with type 2 diabetes both with and without vascular disease (2,4–6). However, despite the proven efficacy of LDL-c lowering in patients with type 2 diabetes, there is still a significant residual risk for cardiovascular events in these patients. For example, despite a 37% reduction in risk in patients randomized to 10 mg atorvastatin per day, in the CARDS trial, with a median follow-up duration of 3.9 years, the absolute risk for a cardiovascular end point remained 5.8% and 4.3% for all-cause mortality (7).

Low HDL-c has been shown to be an independent risk factor for cardiovascular disease in patients with type 2 diabetes and remains a risk factor in patients with type 2 diabetes with stable coronary artery disease and optimal LDL-c control (LDL-c $<$2.6 mmol/L) (8). Elevating plasma HDL-c levels in patients with type 2 diabetes might be effective for further lowering cardiovascular risk, especially in patients with low HDL-c and high TG as shown in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trials (9,10). Recent trials with HDL-c elevating with a cholesteryl ester transfer protein inhibitor or with nicotinic acid, however, have failed to show a reduction in cardiovascular events (11,12). Whether HDL-c levels are indeed still an independent risk factor for (new) cardiovascular disease, even after efficacious LDL-c lowering, remains a matter of discussion (13). The aim of this study is therefore to evaluate whether low HDL-c levels remain a residual risk factor for cardiovascular disease and mortality in patients with type 2 diabetes and attainment of low LDL-c treatment goals and when LDL-c is treated with intensive lipid-lowering therapy.

RESEARCH DESIGN AND METHODS

Patients and Baseline Measurements

For the current study, we used data from all patients with type 2 diabetes enrolled in the Second Manifestations of ARTerial disease (SMART) cohort. This is a prospective ongoing single-center cohort study at the University Medical Center Utrecht among patients with clinically manifest vascular disease or with known important risk factors for atherosclerosis (e.g., diabetes, dyslipidemia, hypertension). All patients between ages 18 and 79 years who were newly referred to the University Medical Center Utrecht for atherosclerotic cardiovascular disease or treatment of cardiovascular risk factors were asked to participate. The rationale and a detailed description of the SMART study has previously been published (14). To summarize, after inclusion, all patients were asked to fill in a questionnaire on history of vascular disease (coronary artery disease, cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm), cardiovascular risk factors (e.g., hypertension, hyperlipidemia, smoking, alcohol consumption, physical activity), and additional medical history. In addition to the questionnaire, the patients underwent physical examination and cardiovascular risk factors were measured (e.g., blood pressure, blood sample for plasma lipids, urine sample for albuminuria, and creatinine excretion). LDL-c was calculated using the Friedewald formula up to plasma triglyceride levels of 9 mmol/L to avoid missing LDL-c (15). Informed consent was obtained from all patients, and the study was approved by the Medical Ethics Committee of the University Medical Center Utrecht. In the current study, data were used from 1,829 patients with type 2 diabetes included between September 1996 and March 2014. Type 2 diabetes was defined as self-reported type 2 diabetes, a referral diagnosis of type 2 diabetes, the use of glucose-lowering medication, or a glucose plasma concentration of $\geq$7.0 mmol/L at baseline with commencement of glucose-lowering therapy within 1 year after inclusion. For exclusion of patients with possible monogenetic causes of very low HDL-c levels, patients with HDL-c levels $<$0.4 mmol/L were excluded (n = 19), leaving 1,810 patients for analyses.

Intensity of Lipid-Lowering Therapy

Data on lipid-lowering therapy were collected for all participants. Categorization in classes of intensity of lipid-lowering therapy was based on theoretical LDL-c reduction. In order to compare the intensity of the different lipid-lowering medication, the theoretical percentage of LDL-c reduction was used. The theoretical percentage of LDL-c reduction was gathered from available literature on the efficacy of statins and other lipid-lowering drugs (16–18). The current study defined intensive lipid-lowering therapy as therapy with a theoretical reduction of $\geq$40% in LDL-c levels (e.g., rosuvastatin in all doses, atorvastatin $\geq$20 mg, and simvastatin $\geq$40 mg). Combination therapy of a statin with ezetimib was taken into account and was regarded as intensive lipid-lowering therapy (e.g., simvastatin + ezetimib 10 mg). A detailed description of the categories in classes of lipid-lowering therapy intensity is shown in Supplementary Table 1.

Follow-up

The study participants receive a questionnaire every 6 months during follow-up in order to obtain information on hospitalization and outpatient clinic visits. All available data were collected on reported events. Death was reported by the general practitioner, treating specialist, or relatives. Three members of the SMART study end point committee independently evaluated the events. Primary outcomes for this study were a composite of major events (myocardial infarction [MI], stroke [ischemic and hemorrhagic], vascular mortality) and all-cause mortality. MI was defined as at least two of the following criteria: *1*) chest pain for at least 20 min, not disappearing after administration of nitrates; *2*) elevation of the ST-segment $>$1 mm in two following leads on an electrocardiogram or a left bundle branch block; and *3*) cardiac enzyme elevation (troponin above clinical cutoff value or creatinine kinase of at least two times the normal value and a myocardial band fraction $>$5% of the total creatinine kinase). Sudden cardiac death was also considered as MI. Vascular mortality was defined as death due to MI, stroke, congestive heart failure, rupture of abdominal aortic aneurysm, and vascular death from other causes. The period between patient inclusion

and first cardiovascular event, death, loss to follow-up, or the predefined date of March 2014 was defined as the follow-up duration. In total, 123 patients (6.8%) were lost to follow-up due to migration or discontinuation of the study.

Data Analyses

Baseline characteristics are presented in quartiles of HDL-c. As females tend to have higher levels of HDL-c, males and females were divided into quartiles of HDL-c and then combined in sex-pooled quartiles. Continuous variables were tested using a one-way ANOVA, and count variables were tested using a χ^2 test.

The association of HDL-c with cardiovascular events and all-cause mortality was evaluated by Cox proportional hazard models. Hazard ratios (HRs) and 95% CIs were calculated for HDL-c as a continuous variable per 0.1 mmol/L increase in HDL-c as well as HDL-c as a group variable with the highest HDL-c quartile as reference category. Three models were used. In model I, the relation between HDL-c and the end point of interest was adjusted for age and sex. In model II, additional adjustment was performed for traditional cardiovascular risk factors: BMI, current smoking, pack-years, current alcohol use, amount of alcohol use, LDL-c, TGs, and systolic blood pressure. Model III was used to adjust for diabetes-specific characteristics: estimated glomerular filtration rate (assessed by MDRD), glucose levels, and HbA_{1c} levels. The variables in the three models are a set of traditional and diabetes-related cardiovascular risk factors based on prior knowledge in literature. A further sensitivity analysis was performed with a model including additional adjustment for albuminuria and antithrombotic therapy at baseline. Patients were censored if they were lost to follow-up.

As missing covariate data and incomplete case analysis lead to loss of statistical power and bias, single imputation methods were used to reduce missing covariate data for BMI (n = 3; 0.2%), current smoking (n = 15; 0.8%), pack-years (n = 14; 0.8%), current alcohol use (n = 19; 1.0%), LDL-c (n = 25; 1.4%), TG (n = 1; 0.06%), systolic blood pressure (n = 11; 0.6%), kidney function estimated by MDRD (n = 3; 0.2%), fasting glucose (n = 7; 0.4%) and HbA_{1c} (n = 131; 7.2%).

For evaluation of whether the relationship between HDL-c and vascular events or all-cause mortality was influenced by intensity of lipid-lowering medication, plasma LDL-c levels, or history of vascular disease, analyses were performed in strata of these variables. For assessment of whether the relationship between HDL-c and cardiovascular events or all-cause mortality was modified by intensity of lipid-lowering medication, plasma LDL-c levels, or history of vascular disease, an interaction term was included in the Cox models. Effect modification was considered to be present if the P value of the interaction term was <0.05.

Analyses were performed using IBM SPSS Statistics and statistical package R 3.1.1. For all analyses, $P < 0.05$ was considered significant.

RESULTS

Baseline Characteristics

Over quartiles of HDL-c, smoking decreased while alcohol consumption increased. In addition, patients with a higher HDL-c had a lower BMI and plasma triglyceride level (Table 1). Medication use was fairly equal across quartiles, with ~60% of the patients receiving lipid-lowering therapy.

Relationship Between HDL-c and Cardiovascular Events and Mortality in Patients With Type 2 Diabetes

A total of 335 new cardiovascular events (MI, ischemic stroke, vascular death) and 385 deaths occurred during a median follow-up of 7.0 years (interquartile range [IQR] 3.9–10.4). In all patients with type 2 diabetes, the risk of MI decreased, with 7% per 0.1 mmol/L increase in HDL-c (adjusted HR 0.93, 95% CI 0.87–1.00), while there was no clear association with any other cardiovascular end point. No relationship was found between HDL-c and all-cause mortality (HR 0.99, 95% CI 0.96–1.03) (data not shown). Similar associations were found when the population was stratified in quartiles of HDL-c (Table 2). The relationship between HDL-c and cardiovascular events or all-cause mortality was the same for patients with type 2 diabetes with and without a history of vascular disease ($P_{interaction}$ = 0.75 and 0.15, respectively). Additional adjustment for the diabetes-specific characteristics in model III did not change the results compared with adjustment for the traditional cardiovascular risk factors in model II (Table 2).

Relationship Between HDL-c and Cardiovascular Events and Mortality According to Intensity of Lipid-Lowering Therapy and Plasma LDL-c Levels

Subgroup analyses showed effect modification by plasma LDL-c levels for the relation between HDL-c and cardiovascular events or all-cause mortality ($P <$ 0.01 for linear interaction term HDL-c*LDL-c for both end points); therefore, the analyses were performed in strata of LDL-c (Table 3). Baseline characteristics for strata of LDL-c are shown in Supplementary Table 2. Major cause of death in all strata according to plasma LDL-c levels was vascular mortality, followed by fatal malignancy (Supplementary Table 3). Higher HDL-c was related to a higher risk of all-cause mortality (HR 1.14, 95% CI 1.07–1.22) in patients with LDL-c levels $<$2.0 mmol/L. In patients with LDL-c levels $<$2.0 mmol/L, a 0.1 mmol/L higher HDL-c is related to a higher risk of vascular mortality (HR 1.12, 95% CI 1.03–1.22). Higher HDL-c was also related to higher risk for cardiovascular events in patients with LDL-c levels $<$2.0 mmol/L (HR 1.10 95% CI 1.02–1.18) in contrast to patients with LDL-c levels between 2.0 and 2.5 mmol/L, where higher HDL-c was related to lower risk (HR 0.85, 95% CI 0.75–0.95). Subgroup analysis in strata of $<$2.0 mmol/L and $>$2.0 mmol/L yielded similar P values for interaction and HRs for the relation between HDL-c and cardiovascular events or mortality (data not shown). Sensitivity analysis with additional adjustment for albuminuria and antithrombotic therapy at baseline did not change the results.

Subgroup analyses did not support effect modification by lipid-lowering therapy for the relation between HDL-c and cardiovascular events or mortality (P = 0.43 and P = 0.12, respectively). In addition, subgroup analyses also did not support effect modification by intensity of lipid-lowering therapy (Supplementary Table 4). However, for the relationship between HDL-c and MI, the P for interaction was borderline significant (P = 0.07). In patients on intensive lipid-lowering therapy, a 0.1 mmol/L increase in HDL-c was related

Table 1—Baseline characteristics according to sex-pooled quartiles of HDL-c

	Sex-pooled quartiles of HDL-c, *N* = 1,810				
	Quartile 1, *n* = 466	Quartile 2, *n* = 471	Quartile 3, *n* = 437	Quartile 4, *n* = 436	*P*
HDL-c range, mmol/L					
Men	0.41–0.88	0.88–1.04	1.04–1.22	1.22–2.85	
Women	0.46–1.02	1.02–1.20	1.20–1.45	1.45–3.00	
Men, *n* (%)	326 (70)	334 (71)	295 (68)	304 (70)	0.73
Age, years	58 ± 10	61 ± 10	61 ± 10	61 ± 10	<0.01
Hypertension, *n* (%)	316 (68)	339 (72)	310 (71)	285 (65)	0.19
Current smoking, *n* (%)	163 (35)	113 (24)	94 (21)	78 (18)	<0.01
Pack-years, median (IQR)	15 (1–34)	14 (1–32)	13 (0–31)	10 (0–28)	0.10
Current alcohol use, *n* (%)	156 (34)	197 (42)	203 (47)	259 (59)	<0.01
Alcohol units per week, *n* (%)					
<1	54 (12)	61 (13)	49 (11)	43 (10)	
1–10	168 (36)	180 (38)	158 (36)	153 (35)	
11–20	55 (12)	62 (13)	85 (20)	86 (20)	
21–30	27 (6)	21 (5)	16 (4)	36 (8)	
31–40	7 (2)	8 (2)	5 (1)	9 (2)	
>40	6 (1)	6 (1)	11 (3)	7 (2)	
Diabetes duration, years, median (IQR)	4 (1–8)	4 (1–10)	4 (1–10)	4 (1–10)	0.05
BMI, kg/m^2	30 ± 5	30 ± 5	29 ± 5	27 ± 4	<0.01
Systolic blood pressure, mmHg	142 ± 20	146 ± 20	147 ± 21	147 ± 22	<0.01
Diastolic blood pressure, mmHg	81 ± 11	83 ± 11	83 ± 12	84 ± 12	<0.01
Laboratory measurements					
Glucose, mmol/L	8.8 ± 3.0	8.8 ± 3.0	8.8 ± 2.9	8.4 ± 2.7	0.10
HbA_{1c}, %	7.2 ± 1.3	7.2 ± 1.3	7.2 ± 1.4	6.9 ± 1.1	<0.01
HbA_{1c}, mmol/mol	55.2 ± 14.2	55.2 ± 14.2	55.2 ± 15.3	51.9 ± 12.0	
eGFR, mL/min/1.73 m^2	79 ± 23	76 ± 22	78 ± 21	79 ± 20	0.07
Microalbuminuria, *n* (%)	110 (24)	112 (24)	114 (26)	90 (21)	0.27
Total cholesterol, mmol/L	4.7 ± 1.4	4.7 ± 1.2	5.0 ± 1.4	4.9 ± 1.3	<0.01
LDL-c, mmol/L	2.6 ± 1.1	2.7 ± 1.1	2.9 ± 1.2	2.7 ± 1.0	<0.01
HDL-c, mmol/L	0.8 ± 0.1	1.0 ± 0.1	1.2 ± 0.1	1.6 ± 0.3	<0.01
Non–HDL-c, mmol/L	3.9 ± 1.4	3.7 ± 1.2	3.8 ± 1.3	3.4 ± 1.3	<0.01
TGs, mmol/L, median (IQR)	2.3 (1.6–3.3)	1.8 (1.4–2.5)	1.6 (1.1–2.3)	1.2 (0.9–1.7)	<0.01
Medication, *n* (%)					
Oral glucose-lowering medication	314 (67)	309 (66)	292 (67)	268 (62)	0.24
Insulin	112 (24)	119 (25)	93 (21)	104 (24)	0.55
β-Blockers	240 (52)	248 (53)	192 (44)	149 (34)	<0.01
ACE inhibitors	189 (41)	203 (43)	158 (36)	154 (35)	0.05
Fibrates	22 (5)	18 (4)	10 (2)	7 (2)	0.03
Nicotinic acid	0 (0)	3 (1)	3 (1)	1 (0)	0.28
Usual-dose lipid-lowering therapy	119 (26)	149 (32)	133 (30)	127 (29)	0.20
Intensive lipid-lowering therapy	153 (33)	161 (34)	134 (31)	132 (30)	0.55
Type of vascular disease, *n* (%)					
Coronary artery disease	216 (46)	221 (47)	185 (42)	176 (40)	0.14
Cerebrovascular disease	89 (19)	91 (19)	89 (20)	76 (17)	0.74
Peripheral artery disease	70 (15)	72 (15)	57 (13)	62 (14)	0.78
Abdominal aortic aneurysm	27 (6)	18 (4)	25 (6)	17 (4)	0.31

Continuous variables are depicted as mean ± SD, count variables as *n* (%), and nonnormally distributed variables as median (IQR). Continuous variables were tested using a one-way ANOVA, and count variables were tested using a χ^2 test. eGFR, estimated glomerular filtration rate by the MDRD equation.

with a 17% higher risk for MI (HR 1.17, 95% CI 1.00–1.37), while in patients on usual dose lipid-lowering therapy a 0.1 mmol/L higher HDL-c was associated with 15% lower risk for MI (HR 0.85, 95% CI 0.74–0.99) (Supplementary Table 4). Again, additional adjustment for the diabetes-specific characteristics in model III did not change the results compared with adjustment for the traditional cardiovascular risk factors in model II (Table 3 and Supplementary Table 4).

CONCLUSIONS

In patients with type 2 diabetes, higher HDL-c levels were related to a lower risk of MI, while there was no clear association with any other cardiovascular end point. The relationship between HDL-c levels and cardiovascular events was, however, dependent of LDL-c levels. In patients with LDL-c plasma levels between 2.0 and 2.5 mmol/L, higher HDL-c levels were related to a lower risk of cardiovascular events. In contrast, patients with type 2 diabetes and LDL-c plasma levels <2.0 mmol/L, higher

Table 2—Relationship between HDL-c and cardiovascular events and mortality in quartiles of HDL-c

	Quartile 1, *n* = 466	Quartile 2, *n* = 471	Quartile 3, *n* = 437	Quartile 4, *n* = 436
HDL-c range, mmol/L				
Men	**0.41–0.88**	**0.88–1.04**	**1.04–1.22**	**1.22–2.85**
Women	**0.46–1.02**	**1.02–1.20**	**1.20–1.45**	**1.45–3.00**
MI				
n	**28**	**40**	**35**	12
Model I	**2.39 (1.21–4.71)**	**3.55 (1.86–6.76)**	**3.02 (1.45–5.43)**	1.00 (ref.)
Model II	2.02 (0.99–4.13)	**3.29 (1.70–6.36)**	**2.75 (1.42–5.34)**	1.00 (ref.)
Model III	2.02 (0.99–4.15)	**3.25 (1.67–6.30)**	**2.82 (1.45–5.49)**	1.00 (ref.)
Ischemic stroke				
n	24	17	18	12
Model I	**2.04 (1.02–4.10)**	1.46 (0.70–3.05)	1.51 (0.73–3.13)	1.00 (ref.)
Model II	1.90 (0.90–4.04)	1.36 (0.64–2.90)	1.39 (0.66–2.91)	1.00 (ref.)
Model III	1.82 (0.86–3.87)	1.23 (0.57–2.63)	1.31 (0.62–2.76)	1.00 (ref.)
Vascular mortality				
n	55	67	43	49
Model I	1.21 (0.82–1.79)	**1.48 (1.02–2.15)**	0.89 (0.59–1.35)	1.00 (ref.)
Model II	1.01 (0.66–1.55)	1.32 (0.90–1.95)	0.79 (0.52–1.20)	1.00 (ref.)
Model III	0.98 (0.64–1.50)	1.21 (0.82–1.78)	0.76 (0.50–1.16)	1.00 (ref.)
Composite of major vascular events				
n	89	**97**	84	65
Model I	**1.50 (1.09–2.08)**	**1.66 (1.21–2.27)**	**1.38 (1.00–1.92)**	1.00 (ref.)
Model II	1.31 (0.92–1.85)	**1.53 (1.10–2.12)**	1.26 (0.91–1.76)	1.00 (ref.)
Model III	1.28 (0.90–1.82)	**1.46 (1.05–2.02)**	1.24 (0.89–1.73)	1.00 (ref.)
All-cause mortality				
n	102	109	87	87
Model I	1.21 (0.90–1.61)	**1.35 (1.02–1.79)**	1.01 (0.75–1.36)	1.00 (ref.)
Model II	1.03 (0.75–1.41)	1.21 (0.90–1.63)	0.90 (0.66–1.22)	1.00 (ref.)
Model III	1.01 (0.74–1.39)	1.12 (0.83–1.50)	0.87 (0.64–1.18)	1.00 (ref.)

HDL-c per quartiles. Quartile 4 = reference (ref.). Data are HR (95% CI). Model 1: age plus sex. Model 2: model 1 adjustments plus BMI, smoking, pack-years, alcohol, LDL-c, TGs, and systolic blood pressure. Model 3: model 2 adjustments plus estimated glomerular filtration rate, glucose, and HbA_{1c}. Boldface data indicate statistically significant values, $P < 0.05$.

HDL-c plasma levels increase the risk for cardiovascular events and all-cause mortality. Intensity of lipid-lowering therapy did not influence the relationship between HDL-c and cardiovascular events or all-cause mortality.

Whether HDL-c remains a risk factor for cardiovascular disease and mortality in patients with type 2 diabetes despite reaching very low LDL-c plasma levels has previously been described. In contrast to our findings, the study performed by Ogita et al. (8) found that low HDL-c is a risk factor for adverse cardiac events despite optimal LDL-c in patients with type 2 diabetes with stable coronary artery disease. However, an optimal LDL-c level was defined as <2.6 mmol/L, and the average LDL-c in that study was 2.1 mmol/L. In concordance, the current study also found that low HDL-c remains a risk factor for cardiovascular events in patients with LDL-c plasma levels between 2.0 and 2.5 mmol/L but not for all-cause mortality. We reported earlier that the relation between HDL-c and vascular risk was irrespective of plasma LDL-c levels in patients with vascular disease, including 17% patients with type 2 diabetes (13). Also, a post hoc analysis of the Treating to New Targets (TNT) trial showed that HDL-c is a risk factor for major cardiovascular events in patients with coronary artery disease treated with statins. The same relation was observed for patients with LDL-c levels <1.8 mmol/L (19). Higher risk for cardiovascular events and mortality with higher HDL-c in patients with type 2 diabetes and very low LDL-c levels, as shown in the current study, was unexpected, and this sharp contrast between our study and earlier findings needs explanation. An obvious clue may lie in the inclusion in our study of only patients with type 2 diabetes and the presumed impaired HDL function in these patients. The notion that an increase in HDL-c is not always beneficial and HDL function may be of greater importance is supported by the recent finding in the dal-OUTCOMES and HPS2-THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events) trials, in which an increase in HDL-c was not associated with a reduction in recurrent cardiovascular events (11,12). It is conceivable that HDL functionality may be of greater importance for the understanding of the relationship between HDL-c and cardiovascular events.

It has previously been described that the apolipoprotein (apo) composition of HDL is altered (20) and that the endothelial-vasoprotective effects of HDL are impaired in patients with type 2 diabetes (20–23). ApoA1 plays a central role in reverse cholesterol transport from macrophages to the liver, and it is frequently reduced in patients with type 2 diabetes (20). This reduction in ApoA1 is caused by reduced synthesis of ApoA1 in the liver and replacement of ApoA1 by serum amyloid A in a chronic inflammation state present in patients with type 2 diabetes (20). Reduced apoA1 can lead to an increased HDL-c–to–apoA1 ratio, which has been found to increase risk for cardiovascular, cancer, and all-cause mortality in the general population (24). Also, elevated plasma levels of serum amyloid A have been found to predict cardiovascular risk (25,26).

The higher risk for cardiovascular events with higher HDL-c in patients with type 2 diabetes and very low LDL-c levels might also be explained by hepatic lipase (HL) and its role in the metabolism of lipoproteins. HL can enhance the selective uptake of HDL-c esters by enzymatic modification of HDL (27). Lipid-lowering treatment in the form of statins, however, not only reduces LDL-c levels but also reduces HL activity (28,29). Higher HDL-c in patients with low LDL-c might therefore be due to HL activity. In addition, low HL activity has been associated to coronary artery disease (30). Therefore, it is conceivable that the increase in HDL-c and increased risk for cardiovascular events both might be due to low HL activity caused by intensive lipid-lowering treatment. This might also explain the increased risk for MI in the intensive lipid-lowering treatment stratum (Supplementary Table 4).

Table 3—Relationship between HDL-c and cardiovascular events and mortality according to plasma LDL-c level

	LDL-c <2.0 mmol/L, *n* = 492	LDL-c 2–2.5 mmol/L, *n* = 492	LDL-c >2.5 mmol/L, *n* = 955	$P_{interaction}$ <2.0 vs. 2.0–2.5/<2.0 vs. >2.5
MI				
n	17	**21**	77	
Model I	0.99 (0.87–1.13)	0.85 (0.71–1.02)	**0.90 (0.83–0.98)**	
Model II	1.01 (0.87–1.17)	**0.80 (0.66–0.98)**	0.93 (0.86–1.02)	
Model III	1.01 (0.87–1.17)	**0.80 (0.65–0.97)**	0.94 (0.86–1.02)	0.07/0.08
Ischemic stroke				
n	9	11	51	
Model I	1.06 (0.89–1.25)	0.80 (0.61–1.05)	**0.88 (0.79–0.98)**	
Model II	0.96 (0.77–1.20)	0.76 (0.57–1.02)	0.92 (0.82–1.02)	
Model III	1.00 (0.79–1.27)	0.75 (0.55–1.02)	0.92 (0.82–1.03)	0.13/0.14
Vascular mortality				
n	**39**	26	149	
Model I	1.07 (0.99–1.15)	0.98 (0.86–1.12)	**0.93 (0.88–0.99)**	
Model II	**1.10 (1.01–1.19)**	0.96 (0.82–1.11)	0.96 (0.91–1.02)	
Model III	**1.12 (1.03–1.22)**	0.94 (0.81–1.10)	0.96 (0.91–1.03)	0.40/0.02
Composite of major vascular events				
n	**58**	**52**	225	
Model I	1.06 (0.99–1.13)	**0.89 (0.80–0.99)**	**0.93 (0.88–0.97)**	
Model II	**1.08 (1.01–1.16)**	**0.86 (0.77–0.97)**	0.95 (0.90–1.00)	
Model III	**1.10 (1.02–1.18)**	**0.85 (0.75–0.95)**	0.96 (0.91–1.00)	0.01/<0.01
All-cause mortality				
n	**68**	62	255	
Model I	**1.09 (1.03–1.16)**	0.98 (0.89–1.07)	**0.92 (0.88–0.96)**	
Model II	**1.13 (1.07–1.20)**	0.98 (0.89–1.09)	**0.94 (0.90–0.99)**	
Model III	**1.14 (1.07–1.21)**	0.98 (0.89–1.09)	**0.94 (0.90–0.99)**	0.09/<0.01

Data are HR (95% CI) per 0.1 mmol/L increase in HDL-c, stratified according to LDL-c plasma levels. Model 1: age plus sex. Model 2: model 1 adjustments plus BMI, smoking, alcohol, TGs, and systolic blood pressure. Model 3: model 2 plus estimated glomerular filtration rate, glucose, and HbA_{1c}. Boldface data indicate statistically significant values, $P < 0.05$.

The higher risk for cardiovascular events with higher HDL-c in patients with type 2 diabetes and very low LDL-c levels could also have been explained by differences in current alcohol use across the LDL-c plasma strata (Supplementary Table 2). Even though alcohol use and the amount of alcohol use were taken into account in analyses, it has to be noted that this was self-reported alcohol use, and therefore the difference in alcohol consumption might still have contributed to the observed relationship between high HDL-c and higher risk for all-cause mortality. Also noteworthy is the analysis based on lipid-lowering therapy intensity. Although not conclusive, this argues against interaction of the more "pleiotropic" effects of statin therapy and argues for a straightforward although not completely understood interaction with reached LDL-c levels. We therefore expect, in a cohort with patients with type 2 diabetes and lipid-lowering therapy consisting of PCSK9 or ezetimib, the presence of the same relationship between HDL-c and cardiovascular events in patients with very low LDL-c.

Strengths of this cohort study are the relevant group of patients with type 2 diabetes, sizeable number of vascular end points, and completeness of data, with a low number of missing data on covariates. Also notable is the low percentage of loss to follow-up (6.8%). In the current study, analyses were extensively adjusted for potential confounders. The third model, consisting of diabetes-specific characteristics, did not change the results, most likely due to overlap in risk factors with the traditional cardiovascular risk factors present in the second model. Study limitations need to be considered, including the fact that only baseline data are available, knowing that risk factor levels and lipid-lowering therapy may have changed over the course of follow-up. The study population consists of high-risk patients with type 2 diabetes, and therefore index event bias could be presumed to play an important role. However, we think this to be less likely, as we found no interaction by presence of vascular disease at baseline on the relation between HDL-c and future cardiovascular disease. A further limitation of this study is the lack of information on HDL function, size, or composition of the HDL particle and HL. Stratification based on lipid-lowering therapy intensity and LDL-c levels resulted in strata with relatively small numbers of events, especially for MIs and ischemic stroke, which may have resulted in reduced precision of risk estimation.

In conclusion, in high-risk patients with type 2 diabetes and very low LDL-c levels, higher HDL-c is related to increased risk of cardiovascular events and all-cause mortality. This is in contrast to high-risk patients with type 2 diabetes and LDL-c levels between 2.0 and 2.5 mmol/L, where higher HDL-c is related to a decreased risk of cardiovascular events. Future studies are needed to confirm this finding and investigate the causality as the issue of very low LDL-c– and HDL-c–dependent cardiovascular risk becomes more relevant in an upcoming era of even more potent LDL-c–lowering therapy.

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