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Low High-Density Lipoprotein Cholesterol Is Not a Risk Factor for Recurrent Vascular Events in Patients With Vascular Disease on Intensive Lipid-Lowering Medication

Anton P. van de Woestijne, MD,* Yolanda van der Graaf, MD, PhD,† An-Ho Liem, MD, PhD,‡ Maarten J. M. Cramer, MD, PhD,§ Jan Westerink, MD, PhD,* Frank L. J. Visseren, MD, PhD,* for the SMART Study Group

Utrecht and Rotterdam, the Netherlands

Objectives This study sought to evaluate the vascular risk of low high-density lipoprotein-cholesterol (HDL-C) in relation to the use and intensity of lipid-lowering medication in patients with clinically manifest vascular diseases.

Background Low levels of HDL-C are associated with an increased risk for vascular diseases and may contribute to residual vascular risk in patients already treated for other risk factors. However, post-hoc analyses from statin trials indicate that the vascular risk associated with low HDL-C may be low or even absent in patients using intensive statin therapy.

Methods We performed a prospective cohort study of 6,111 patients with manifest vascular disease. Cox proportional hazards models were used to evaluate the risk of HDL-C on vascular events in patients using no, usual dose, or intensive lipid-lowering therapy.

Results New vascular events (myocardial infarction, stroke, or vascular death) occurred in 874 subjects during a median follow-up of 5.4 years (interquartile range: 2.9 to 8.6 years). In patients not using lipid-lowering medication at baseline (n = 2,153), a 0.1 mmol/l increase in HDL-C was associated with a 5% reduced risk for all vascular events (hazard ratio [HR]: 0.95; 95% confidence interval [CI]: 0.92 to 0.99). In patients on usual dose lipid-lowering medication (n = 1,910) there was a 6% reduced risk (HR: 0.94; 95% CI: 0.90 to 0.98). However, in patients using intensive lipid-lowering treatment (n = 2,046), HDL-C was not associated with recurrent vascular events (HR: 1.02; 95% CI: 0.98 to 1.07) irrespective of low-density lipoprotein cholesterol level.

Conclusions In patients with clinically manifest vascular disease using no or usual dose lipid-lowering medication, low plasma HDL-C levels are related to increased vascular risk, whereas in patients using intensive lipid-lowering medication, HDL-C levels are not related to vascular risk. (J Am Coll Cardiol 2013;62:1834–41) © 2013 by the American College of Cardiology Foundation

Low levels of high-density lipoprotein-cholesterol (HDL-C) are recognized as an important risk factor for vascular disease, both in healthy populations (1–3) and in patients with known vascular disease (4–6). Although patients with clinically manifest vascular disease are usually intensively treated for risk factors such as high levels of low-density lipoprotein-cholesterol (LDL-C), these patients are still at a high residual risk for vascular events. Low HDL-C is a risk factor for vascular disease independent of LDL-C (7), even when LDL-C is at target level, and this is still apparent in patients with vascular disease (4,6,8). However, in a recent analysis of the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial (9), the inverse association

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From the *Department of Vascular Medicine, University Medical Center Utrecht, Utrecht, the Netherlands; †Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands; ‡Department of Cardiology, Sint Franciscus Gasthuis, Rotterdam, the Netherlands; and the §Department of Cardiology, University Medical Center Utrecht, Utrecht, the Netherlands. The SMART study was financially supported by a grant of the University Medical Centre Utrecht. Dr. Visseren's department receives grant support from the Netherlands Organisation for Health Research and Development and the Catharijne Foundation Utrecht; and speaker fees from Merck. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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between HDL-C and vascular events was not observed in patients using intensive statin therapy in the primary prevention setting. Although these results have been disputed (10,11), statin trials in patients with coronary artery disease have seen a similar lack of the inverse relation between HDL-C and risk of vascular events in patients receiving (intensive) statin therapy (12,13). Thus far, findings concerning the absence of increased risk with low HDL-C levels primarily come from statin trials, in which patients are treated with a fixed statin dose. However, this is not a reflection of clinical practice as, according to current guidelines, LDL-C is treated to target, with various dosages of different statins including combination therapy. However, as many patients with clinically manifest vascular disease are treated with statins, the residual risk from HDL-C in these patients may be smaller than initially thought. Currently, pharmacologic methods to increase HDL-C, such as cholesteryl ester transfer protein (CETP) inhibition, are investigated for their potential ability to further decrease vascular risk in addition to intensive statin therapy in patients with vascular disease (14), but the results of CETP inhibitors in terms of reduction in vascular risk are as yet disappointing. The CETP inhibitor dalcetrapib did not show a beneficial effect on endothelial function (15) or vascular events (16) when added to statin therapy, despite a 30% increase in HDL-C. Also, the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) (17) study, in which extended release niacin was added to intensive statin therapy to increase HDL-C, did not show beneficial results, although the increase in HDL-C was only modest in this trial. The results of the HPS2 THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events) trial, comparing extended release niacin/laropiprant and statin therapy (including ezetimibe if necessary) with statin (including ezetimibe if necessary), also showed no beneficial effects of niacin when added to statin therapy (18,19).

In the present study, we evaluated the risk associated with plasma levels of HDL-C in patients with clinical manifestations of vascular disease with or without lipid-lowering therapy. Furthermore, we evaluated the influence of the intensity of treatment on the relation between HDL-C and vascular events and whether this is influenced by achieved levels of LDL-C.

Methods

Patients. Data were used from patients enrolled in the SMART (Second Manifestation of ARTerial disease) cohort. This is a prospective, ongoing cohort study at the University Medical Center Utrecht, the Netherlands, designed to study the presence of concomitant arterial diseases and risk factors for atherosclerosis in a high-risk population. Patients newly referred to our institution with clinically evident vascular disease or a vascular risk factor (hyperlipidemia, hypertension, or diabetes) were asked to participate. Written informed consent was obtained from all patients. The Medical Ethics Committee of the University Medical Center Utrecht approved the study.

Abbreviations and Acronyms

BMI = body mass index
CETP = cholesteryl ester transfer protein
CI = confidence interval
HDL-C = high-density lipoprotein-cholesterol
HR = hazard ratio
LDL-C = low-density lipoprotein-cholesterol
TG = triglycerides

After inclusion, all patients underwent a vascular screening protocol including a health questionnaire, laboratory measurements, and physical examination. A detailed description of the study design has been published previously (20).

For the present study, data were used from 6,123 patients enrolled in the SMART study between September 1996 and March 2011 with either a history or a recent diagnosis of clinically manifest arterial disease: coronary artery disease, cerebrovascular disease, peripheral artery disease, or aneurysm of the abdominal aorta. Patients could be classified into more than 1 disease category. Patients with HDL-C >3.0 or <0.4 mmol/l were excluded (n = 12) to exclude patients with monogenetic causes of low or high HDL-C; hence, the study population consisted of 6,111 patients.

Single imputation methods were used to reduce missing covariate data for smoking (n = 26; 0.4%), alcohol use (n = 29; 0.5%), body mass index (BMI) (n = 10; 0.2%), total cholesterol (n = 1; 0.02%) and plasma triglycerides (TG) (n = 2; 0.03%), since complete case analysis leads to loss of statistical power and to bias.

Laboratory assessment. Baseline lipid levels were obtained from fasting patients. Plasma total cholesterol and TG were measured using commercial enzymatic dry chemistry kits (Johnson & Johnson, New Brunswick, New Jersey). HDL-C in plasma was determined using a commercial enzymatic kit (Boehringer-Mannheim, Mannheim, Germany) after precipitation of LDL-C and very low-density lipoprotein cholesterol with sodium phosphotungstate magnesium chloride. LDL-C was calculated using the Friedewald formula up to a plasma TG level of 9 mmol/l, which is in line with data showing that the Friedewald formula can be used up to this level (21), to avoid many missing values in the low HDL-C category. Calculated LDL-C levels <0.5 mmol/l were regarded as unreliable and not used for analyses. As a result, LDL-C levels could be calculated for 6,085 of 6,111 patients (99.6%).

Coding of lipid-lowering medication. Type and dose of lipid-lowering therapy was registered for all participants. To compare the intensity of different types of drugs, the theoretical percentage of LDL-C reduction per individual type and dose of lipid-lowering therapy was determined, based on (systematic) reviews and meta-analyses to the efficacy of statins and other lipid-lowering drugs (22–24). For the

present study, intensive lipid-lowering medication was defined as lipid-lowering medication theoretically lowering LDL-C ≥40%. This implies that, for example, pravastatin and fluvastatin will not fall in the intensive lipid-lowering group at any dose, whereas rosuvastatin will be defined as intensive lipid-lowering therapy in all doses. For atorvastatin and simvastatin, this will depend on the dose used, with ≥20 mg atorvastatin and ≥40 mg simvastatin being considered intensive lipid-lowering therapy. Furthermore, we accounted for the addition of other lipid-lowering drugs. For example, combination therapy with ezetimibe 10 mg was also regarded as intensive therapy, since this was only used in combination with simvastatin and atorvastatin. Besides this, categories of lipid-lowering therapy were defined according to theoretical LDL-C reduction. This resulted in 4 categories, with reductions of 1% to <30% (category 1), 30% to <40% (category 2), 40% to <45% (category 3), and ≥45% (category 4). Detailed information about these categories is shown in Online Table 1.

Follow-up. All study participants received a questionnaire every 6 months during the follow-up period to obtain information about hospitalizations and outpatient clinic visits. All available relevant data from any reported possible event were collected. Death of a participant was reported by relatives, the general practitioner, or the specialist who treated the participant. All events were classified independently by 3 members of the SMART Study Endpoint Committee, which comprised physicians from different departments. The outcomes of interest for this study were a composite of vascular death, myocardial infarction, or ischemic stroke (a definition of these outcomes is shown in Online Table 2). Follow-up duration (years) was defined as the period between study inclusion and first cardiovascular event or death from any cause, date of loss to follow-up, or the pre-selected date of March 1, 2011.

Data analysis. Baseline characteristics are presented according to quartiles of HDL-C. Male and female patients were divided separately into HDL-C quartiles and then combined (sex-pooled quartiles) to prevent over-representation of females in the highest HDL-C quartiles.

The effect of plasma HDL-C levels on the occurrence of vascular events was evaluated using Cox proportional hazards models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for HDL-C as a continuous variable per 0.1 mmol/l increase in HDL-C. The HRs were adjusted for age and sex in model 1, with additional adjustment for type 2 diabetes mellitus, BMI, and plasma TG in model 2, all of which may confound the relationship between plasma HDL-C and vascular events. In model 3, model 2 was additionally adjusted for current smoking and use of alcohol. In an exploratory analysis, we adjusted for all baseline factors (model 4: model 3 + localization of vascular disease, systolic blood pressure, estimated glomerular filtration rate, and LDL-C). Analyses were performed using the endpoints of myocardial infarction, ischemic stroke, vascular death, and a composite endpoint of all vascular events, which was comprised of myocardial infarction, stroke, and vascular death. Patients were censored if they were lost to follow-up (3.8%). To investigate whether the effect of HDL-C on vascular events was influenced by the use of (intensive) lipid-lowering medication, these analyses were stratified into patients using no lipid-lowering medication, using nonintensive lipid-lowering medication, or using intensive lipid-lowering medication.

To identify whether LDL-C level influenced the effect of HDL-C on vascular events and whether a potential modification by lipid-lowering medication could be explained by the LDL-C lowering effect, additional analyses were performed with stratification for LDL-C level at cutoff values of 2.0, 2.5, 3.0, and 4.0 mmol/l.

Additionally, the above analyses were visualized by calculating the HR for increasing quartiles of HDL-C in strata of lipid-lowering medication or LDL-C level.

Finally, we divided the lipid-lowering therapy into 4 categories based on the amount of LDL-C reduction to estimate an HR for HDL-C in these categories (categories: lipid-lowering medication reducing LDL-C <30%, 30% to <40%, 40% to <45%, and ≥45%).

To test for interaction, that is, whether the relation between plasma HDL-C levels and vascular events was modified by the use of (intensive) lipid-lowering medication or LDL-C level, we included an interaction term in the Cox model. If the p value of the interaction term was < 0.05, effect modification was considered to be present. Since the difference in baseline characteristics between the groups using no lipid-lowering therapy, usual dose lipid-lowering therapy, and intensive lipid-lowering therapy could possibly explain a differential effect of HDL-C in the different strata, we constructed a propensity score to adjust for these between-group differences. We constructed a propensity score for use of lipid-lowering therapy in general and a propensity score for use of intensive lipid-lowering therapy using all baseline characteristics (also including use of antiplatelet agents or blood pressure lowering agents and time since inclusion) for this propensity score. The Cox model adjusted for age, sex, type 2 diabetes mellitus, body mass index, plasma triglycerides, smoking, alcohol usage, LDL-C level, and the propensity score.

The proportional hazard assumption for the Cox model was tested using scaled Schoenfeld residuals, confirming proportional hazards. Only in patients using non-intensive lipid-lowering medication, the proportional hazard assumption did not hold overall due to non-proportional hazards for age. In these patients, the HR should be interpreted as an average over time.

Analyses were performed using statistical package R 2.13 (R Core Team, Vienna, Austria). For all analyses, $p < 0.05$ was considered significant.

Results

Baseline characteristics. With increasing quartiles of HDL-C, the mean BMI and waist circumference declined

Table 1 Baseline Characteristics According to Sex-Pooled Quartiles of HDL-C

	Quartile 1 (n = 1,560)	Quartile 2 (n = 1,514)	Quartile 3 (n = 1,523)	Quartile 4 (n = 1,514)	p Value
HDL-C (mmol/l)	0.85 ± 0.12	1.08 ± 0.12	1.28 ± 0.14	1.68 ± 0.31	
Male	0.41–0.93	0.94–1.10	1.11–1.32	1.33–2.94	
Female	0.50–1.12	1.13–1.36	1.37–1.64	1.65–2.94	
Age (yrs)	58.4 ± 10.6	60.1 ± 10.2	60.2 ± 10.4	61.5 ± 10.2	<0.01
Male	1,169 (75)	1,105 (73)	1,134 (75)	1,134 (75)	0.57
BMI (kg/m^2)	28.1 ± 4.3	27.1 ± 3.8	26.6 ± 3.8	25.5 ± 3.5	<0.01
Waist circumference* (cm)	99.3 ± 11.9	96.4 ± 11.6	95.1 ± 11.2	92.0 ± 11.6	<0.01
Metabolic syndrome	1,353 (87)	999 (66)	564 (37)	345 (23)	<0.01
Type 2 diabetes mellitus	370 (24)	287 (19)	216 (14)	149 (10)	<0.01
Systolic blood pressure (mm Hg)	139 ± 21	141 ± 21	141 ± 21	144 ± 21	<0.01
Diastolic blood pressure (mm Hg)	81 ± 11	81 ± 11	81 ± 11	83 ± 11	<0.01
Total cholesterol (mmol/l)	4.8 ± 1.3	4.9 ± 1.2	4.9 ± 1.1	5.1 ± 1.1	<0.01
LDL-C (mmol/l)	3.0 ± 1.1	3.0 ± 1.1	2.9 ± 1.0	2.8 ± 1.0	<0.01
Triglycerides (mmol/l)	2.3 ± 1.4	1.7 ± 1.1	1.6 ± 1.3	1.2 ± 0.7	<0.01
eGFR (ml/min/1.73 m^2)†	75 ± 19	75 ± 18	76 ± 17	77 ± 18	0.04
Alcohol use during last year	953 (61)	1,000 (66)	1,114 (73)	1,250 (83)	<0.01
Current smoking	628 (40)	512 (34)	453 (30)	425 (28)	<0.01
Lipid-lowering medication	956 (61)	997 (66)	1,026 (67)	979 (65)	<0.01
Intensive lipid-lowering medication‡	484 (31)	520 (34)	544 (36)	498 (33)	0.04
Localization of vascular disease					
Coronary artery disease	961 (62)	979 (65)	928 (61)	819 (54)	<0.01
Cerebrovascular disease	427 (27)	368 (24)	453 (30)	503 (33)	<0.01
Peripheral arterial disease	362 (23)	311 (21)	262 (17)	298 (20)	<0.01
Abdominal aortic aneurysm	157 (10)	138 (9)	123 (8)	124 (8)	0.18

Values are mean ± SD, range, or n (%). *Available for patients included from 1999 onwards. †Glomerular filtration rate, as estimated by the Modification of Diet in Renal Disease (MDRD) equation. ‡Defined as lipid-lowering medication lowering LDL-C with 40%.

BMI = body mass index; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol.

and the prevalence of the metabolic syndrome and type 2 diabetes mellitus was lower (Table 1). The proportion of patients using lipid-lowering medication was approximately 65%, and this did not differ across HDL-C quartiles. Almost two-thirds of patients had coronary artery disease, although the frequency was slightly lower in the highest quartile of HDL-C. About one-third of the patients had cerebrovascular disease.

Plasma HDL-C and the risk of recurrent vascular events according to use of lipid-lowering medication. Median follow-up was 5.4 years (interquartile range: 2.9 to 8.6 years). During this follow-up, 874 new vascular events occurred (myocardial infarction, stroke, and vascular death). Per 0.1 mmol/l increase in HDL-C, the risk of vascular events decreased 5% (HR: 0.95; 95% CI: 0.92 to 0.99) in patients not using lipid-lowering medication (Table 2). Additional adjustment for baseline factors in model 4 did not affect this relation. Similar relations were seen between HDL-C and myocardial infarction (HR: 0.93; 95% CI: 0.88 to 0.97), ischemic stroke (HR: 0.95; 95% CI: 0.89 to 1.01), and vascular death (HR: 0.97; 95% CI: 0.93 to 1.01).

In patients on usual dose lipid-lowering therapy (n = 1,910), the risk for all vascular events per 0.1 mmol/l increase in HDL-C decreased 6% (HR: 0.94; 95% CI: 0.90 to 0.98) (Table 2). However, in patients using intensive lipid-lowering medication, HDL-C plasma levels were not associated with vascular events (HR: 1.02; 95% CI: 0.98 to 1.07). Furthermore, HDL-C was not associated with myocardial infarction (HR: 0.99; 95% CI: 0.93 to 1.07), ischemic stroke (HR: 1.01; 95% CI: 0.93 to 1.10), or vascular death (HR: 1.07; 95% CI: 1.00 to 1.16). The p for interaction in model 3, after additional adjustment for a possible differential effect of LDL-C level and propensity score, was 0.03, indicating modification of the effect of HDL-C by intensive lipid-lowering treatment, irrespective of LDL-C or baseline differences between the groups. In quartiles of higher HDL-C, the risk of vascular events was lower in patients on usual dose lipid-lowering therapy compared with the lowest HDL-C quartile (Fig. 1A). For patients on intensive lipid-lowering therapy, the overall risk for vascular events is lower compared with patients using no or usual dose lipid-lowering, but there was no relation between HDL-C and vascular risk in that group (Fig. 1B). An association between HDL-C and vascular events in patients on intensive lipid-lowering therapy was absent independent of the year of inclusion and was absent both in patients with low levels of CRP (<2 mg/l) or high levels of CRP (≥2 mg/l). Analyses only based on statin treatment instead of lipid-lowering therapy in general did not change the results.

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Table 2 Risk of Vascular Events by HDL-C According to Lipid-Lowering Treatment

	No Lipid-Lowering (n = 2,153)	Usual Dose Lipid-Lowering (n = 1,910)	Intensive Lipid-Lowering (n = 2,046)
All vascular events	454	262	158
Model 1	0.95 (0.92–0.97)	0.93 (0.89–0.97)	0.99 (0.95–1.04)
Model 2	0.95 (0.92–0.98)	0.93 (0.89–0.97)	1.00 (0.96–1.05)
Model 3	0.95 (0.92–0.99)	0.94 (0.90–0.98)	1.02 (0.98–1.07)
Model 4	0.96 (0.93–1.00)	0.94 (0.90–0.98)	1.03 (0.98–1.08)
Myocardial infarction	222	157	79
Model 1	0.92 (0.88–0.96)	0.90 (0.85–0.95)	0.98 (0.91–1.04)
Model 2	0.93 (0.88–0.97)	0.90 (0.85–0.96)	0.98 (0.91–1.05)
Model 3	0.93 (0.88–0.97)	0.91 (0.85–0.97)	0.99 (0.93–1.07)
Model 4	0.93 (0.89–0.98)	0.91 (0.86–0.97)	1.00 (0.93–1.08)
Ischemic stroke	108	61	49
Model 1	0.96 (0.90–1.01)	0.95 (0.87–1.03)	0.98 (0.90–1.06)
Model 2	0.95 (0.89–1.02)	0.96 (0.88–1.05)	0.99 (0.91–1.07)
Model 3	0.95 (0.89–1.01)	0.97 (0.88–1.06)	1.01 (0.93–1.10)
Model 4	0.96 (0.90–1.03)	0.96 (0.88–1.06)	1.00 (0.91–1.09)
Vascular death	312	131	69
Model 1	0.95 (0.92–0.99)	0.90 (0.85–0.96)	1.04 (0.98–1.11)
Model 2	0.97 (0.93–1.01)	0.91 (0.85–0.97)	1.05 (0.98–1.13)
Model 3	0.97 (0.93–1.01)	0.91 (0.85–0.98)	1.07 (1.00–1.15)
Model 4	0.98 (0.94–1.02)	0.92 (0.86–0.98)	1.09 (1.01–1.17)

Values are number of events or hazard ratio (95% confidence interval) per 0.1 mmol/l increase in HDL-C, stratified for no lipid-lowering therapy, usual dose (e.g., pravastatin, atorvastatin 10 mg), or intensive lipid-lowering therapy (e.g., atorvastatin 20 to 80 mg, rosuvastatin). Model 1: Adjusted for age and sex. Model 2: Model 1 + type 2 diabetes mellitus, body mass index, and plasma triglyceride levels. Model 3: Model 2 + smoking and alcohol. Model 4: Model 3 + localization of vascular disease, systolic blood pressure, eGFR, and LDL-C.

Abbreviations as in Table 1.

Plasma HDL-C and the risk of recurrent vascular events according to LDL-C level. The relation between HDL-C and risk for vascular events was not modified by LDL-C (p for interaction = 0.3). Table 3 shows the HR per 0.1 mmol/l increase in HDL-C at different LDL-C levels, stratified for use of lipid-lowering medication. In patients using lipid-lowering medication, HDL-C was not related to risk of vascular events at LDL-C levels <2.0 mmol/l. Of these patients, 70% used intensive lipid-lowering medication. In patients with LDL-C ≥2.0 mmol/l, increasing HDL-C levels were related to a lower vascular risk. Adjustment for all baseline factors did not change the results (data not shown), although the number of events may not be sufficient in all strata to allow firm conclusions.

Plasma HDL-C and the risk of recurrent vascular events according to intensity of lipid-lowering therapy. The intensity of lipid-lowering therapy modified the relation between HDL-C and vascular events (Table 4). In patients using lipid-lowering therapy that lowers LDL-C <30%, the risk for vascular events was 5% lower (HR: 0.95; 95% CI: 0.88 to 1.02) for each 0.1 mmol/l increase in HDL-C. The inverse association between HDL-C and vascular events gradually changed with increasing intensity of lipid-lowering medication. In patients on lipid-lowering therapy that is considered to lower LDL-C >45%, there was no relation between HDL-C and vascular events (HR: 1.06; 95% CI: 0.99 to 1.15). The p for interaction by intensity of lipid-lowering therapy was 0.03. Adjustment for all baseline factors did not change the results (data not shown).

Discussion

In patients with clinically manifest vascular disease not treated with lipid-lowering medication or treated with usual dose lipid-lowering medication, low HDL-C was associated with an increased risk of recurrent vascular events; in contrast, in patients on intensive dose lipid-lowering therapy, HDL-C was not associated with vascular events. The plasma level of LDL-C did not modify the effect of HDL-C on vascular events.

Low plasma HDL-C is recognized as a risk factor for (recurrent) vascular events (1–4), and our results confirm these findings for patients using no or usual dose lipid-lowering therapy. However, several trials such as JUPITER (9), CARE (Cholesterol and Recurrent Events) (12), and PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) (13), report absence of an association between low HDL-C and vascular events in patients with and without vascular disease on statin therapy. An important difference between these trials and clinical practice is the fixed statin dose used in trials instead of treating to a target, as is advocated in European and American treatment guidelines (25,26). In a recent report from the Crusade registry, HDL-C was also not associated with recurrent myocardial infarction or death in patients with myocardial infarction on statin therapy, but type and dose of statin therapy was not specified (27). Our study is a real-life situation in which patients are treated to an LDL-C target, as advocated in

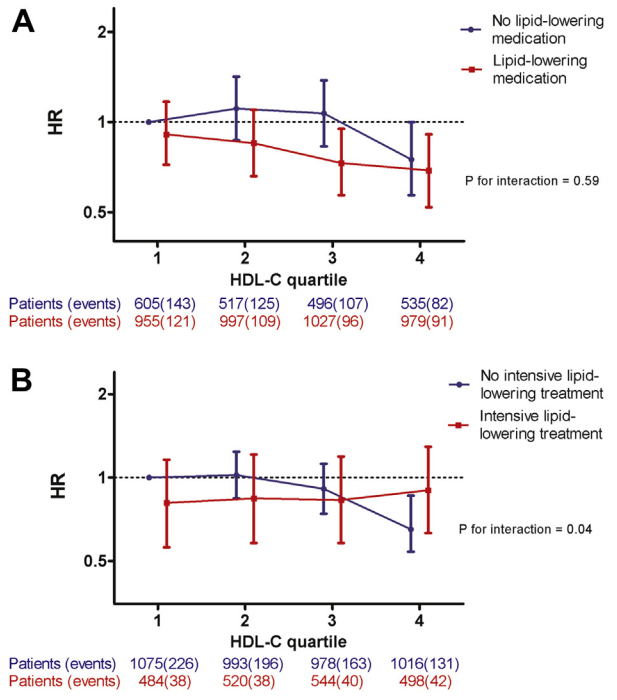

Figure 1 Risk for All Vascular Events Across Quartiles of HDL-C

(A) Hazard ratio (HR) (95% confidence interval) by increasing quartiles of high-density lipoprotein cholesterol (HDL-C), stratified for yes versus no lipid-lowering therapy, adjusted for age, sex, body mass index, type 2 diabetes mellitus, plasma triglyceride level, alcohol use, and smoking. **(B)** HR (95% confidence interval) by increasing quartiles of HDL-C, stratified for yes versus no intensive lipid-lowering therapy (defined as ≥40% low-density lipoprotein cholesterol reduction), adjusted for age, sex, body mass index, type 2 diabetes mellitus, plasma triglyceride level, alcohol use, and smoking. The reference group includes both patients using no lipid-lowering medication and patients using usual dose lipid-lowering medication.

clinical guidelines, with information about different doses and types of lipid-lowering medication that were used, in contrast to a single fixed dose in clinical trials. We are able to evaluate a wide range of different lipid-lowering medication, instead of comparing 2 different doses or comparing a single dose with placebo. Therefore, we could demonstrate a gradual decrease of the inverse association between HDL-C and outcomes with increasing intensity of lipid-lowering treatment. This observation is consistent with a report from the TNT (Treating to New Targets) trial (28), in which HDL-C was associated with vascular events in the atorvastatin 10 mg group, whereas it was not associated with vascular events in the atorvastatin 80 mg group. Our results obtained in a cohort study indicate that not merely statin treatment, but also treatment intensity affects the relation between HDL-C plasma concentrations and vascular risk. In contrast to our findings, other cohort studies in patients with vascular disease treated with statins according to current guidelines have reported that HDL-C was still inversely associated with vascular events (8,29). However, intensity of lipid-lowering therapy was not reported, and the average LDL-C reduction of 28% (8) and/or the reached LDL-C level of approximately 130 mg/dl (3.4 mmol/l) (29) suggests that not all patients were on intensive statin therapy. In the present real-life study, all lipid-lowering therapy, mainly statins and cholesterol absorption inhibitors, were taken into account to estimate an expected proportion of LDL-C reduction as a measure of intensity of lipid-lowering treatment. Previous reports about lipid-lowering treatment modifying the relation between HDL-C and vascular events specifically only considered statin therapy. The lipid-lowering treatment used in the present study was also primarily statin therapy, and, therefore, these results can be compared with previous reports in statin-treated patients. In a sensitivity analysis, performing analyses only based on statin treatment did not change the results.

In concordance with our results, studies in patients with and without vascular disease have shown that low HDL-C levels are related to increased vascular risk irrespective of plasma LDL-C level (4,7), even at LDL-C <1.8 mmol/l (28,30). The present study confirms these findings, although few patients reached very low LDL-C levels without receiving intensive statin therapy. The association between HDL-C and vascular events was not modified by LDL-C level. The inverse association between HDL-C and vascular events was not present only in patients with LDL-C <2 mmol/l on lipid-lowering therapy, and this is consistent

Table 3 Risk of Vascular Events by HDL-C According to LDL-C Level

LDL-C (mmol/l)	<2.0	2.0 to <2.5	2.5 to <3.0	3.0 to <4.0	≥4.0
Lipid-lowering therapy	1,027 (79)	997 (84)	861 (88)	803 (123)	250 (42)
Model 1	1.01 (0.95–1.07)	0.96 (0.90–1.03)	0.97 (0.91–1.04)	0.90 (0.84–0.96)	0.93 (0.84–1.04)
Model 2	1.00 (0.94–1.07)	0.97 (0.90–1.04)	0.98 (0.91–1.06)	0.91 (0.84–0.98)	0.94 (0.85–1.06)
Model 3	1.02 (0.95–1.09)	0.97 (0.90–1.05)	1.01 (0.94–1.09)	0.92 (0.86–0.99)	0.96 (0.86–1.07)
No lipid-lowering therapy		297 (43)	301 (46)	812 (180)	737 (183)
Model 1		0.95 (0.87–1.03)	0.97 (0.90–1.05)	0.95 (0.90–1.00)	0.94 (0.89–0.99)
Model 2		0.94 (0.85–1.03)	0.97 (0.90–1.06)	0.97 (0.91–1.02)	0.93 (0.88–0.99)
Model 3		0.94 (0.86–1.04)	0.98 (0.90–1.07)	0.97 (0.92–1.02)	0.94 (0.89–1.00)

Values are n (events) or hazard ratio (95% confidence interval) per 0.1 mmol/l increase in HDL-C, stratified for LDL-C level separately for use of lipid-lowering therapy. For patients using no lipid-lowering therapy, few patients (n = 124) had LDL-C levels <2.0 mmol/l; therefore, these patients were added to the patients with LDL-C levels of 2.0 to <2.5 mmol/l. Model 1: Adjusted for age and sex. Model 2: Model 1 + type 2 diabetes mellitus, body mass index, and plasma triglyceride levels. Model 3: Model 2 + smoking and alcohol.

Abbreviations as in Table 1.

Table 4 Risk of Vascular Events by HDL-C in Categories of Increasingly Potent Lipid-Lowering Therapy

Category of Lipid-Lowering Therapy	n (Events)	LDL-C Level (mmol/l)	Risk for Vascular Events Per 0.1 mmol/l Increase		
			Model 1	Model 2	Model 3
1 (1% to <30%)	763 (114)	2.9 ± 0.8	0.92 (0.86–0.98)	0.93 (0.87–1.00)	0.95 (0.88–1.02)
2 (30% to <40%)	1,144 (148)	2.7 ± 0.8	0.93 (0.88–0.99)	0.93 (0.88–0.99)	0.94 (0.88–1.00)
3 (40% to <45%)	1,310 (92)	2.4 ± 0.8	0.98 (0.92–1.04)	0.99 (0.93–1.05)	1.01 (0.95–1.07)
4 (≥45%)	735 (65)	2.3 ± 0.9	1.02 (0.95–1.10)	1.04 (0.97–1.13)	1.06 (0.99–1.15)
p value for interaction lipid-lowering therapy × HDL-C			0.03	0.03	0.03

Categories of lipid-lowering therapy were defined according to theoretical LDL-C reduction: 1% to <30%, 30% to <40%, 40% to <45%, and <45%. Model 1: adjusted for age and sex. Model 2: Model 1 + type 2 diabetes mellitus, body mass index, and plasma triglyceride levels. Model 3: Model 2 + smoking and alcohol.
Abbreviations as in Table 1.

with the high prevalence of intensive lipid-lowering treatment in this group.

Although all patients in our study would qualify for treatment with lipid-lowering treatment, a part of these patients was not treated at baseline. These patients were generally included earlier in this study, which started in 1996, when the use of lipid-lowering therapy was lower. In addition, in patients with cerebrovascular disease, peripheral arterial disease, or an abdominal aortic aneurysm, the use of lipid-lowering therapy was generally lower at baseline compared with patients with coronary artery disease. However, the propensity score also included year of inclusion and localization of disease, and the p for interaction was still statistically significant after adjustment for a differential effect of these factors and the other baseline variables included in the propensity score.

Our results do not allow conclusions about the possible effect of HDL-C raising therapy in a population of patients with vascular disease. Randomized controlled trials are necessary to evaluate the effect of HDL-C raising therapy in these patients. Although a Mendelian randomization study indicated that HDL-C as such may not be a causal factor in vascular disease (31), and previous trials with CETP inhibitors (16,32) or niacin (17–19) to increase HDL-C in addition to intensive statin treatment showed no reduction of cardiovascular events, the new CETP inhibitors anacetrapib and evacetrapib also reduce LDL-C and may, therefore, lower cardiovascular risk due to LDL-C reduction. In addition, interventions targeted at increasing HDL-C that also affect HDL function could still be beneficial in patients with vascular disease. However, the results of the present study indicate that in patients using intensive statin therapy, HDL-C may not be a good secondary treatment target, and these results could provide an alternative explanation for the failure of CETP inhibitors to show any benefit in addition to intensive statin treatment. Explanations for the apparent absence of a relation between HDL-C and vascular events in patients treated with intensive lipid-lowering therapy can only be speculated upon. Although statins marginally increase HDL-C depending on type and dose and beneficially influence several molecules in HDL metabolism such as CETP, lipoprotein lipase, and paraoxonase-1 (33), the consequences of these effects on HDL function remain poorly understood. Whether the results of the present study can be explained by functional changes in HDL during intensive statin therapy, whether the relation between HDL function and plasma HDL-C level is lost in intensive statin therapy, or whether anti-inflammatory and antioxidant properties of HDL-C are less relevant as high-dose statin therapy already exerts anti-inflammatory and antioxidant actions is not known.

Study limitations. Plasma lipid levels were measured only once at the start of the study. Moreover, only data about baseline medication was available, which is likely to have changed during follow-up. It is likely that the number of patients receiving lipid-lowering therapy and the proportion of patients receiving intensive lipid-lowering treatment during follow-up has increased. Most patients receiving intensive statin therapy already at baseline are likely to continue use of intensive therapy during follow-up. Therefore, a "drop-in" of lipid-lowering therapy in the patients not using lipid-lowering therapy at baseline would likely only decrease the difference between the groups and, hence, lead to an underestimation of the difference in effect of HDL-C in patients using or not using intensive lipid-lowering therapy. Second, stratification of our study population in different LDL-C categories resulted in a small number of events in some groups, attenuating the precision of the risk estimation. Drawing firm conclusions from the results in different LDL-C categories should therefore be done with caution, but these analyses serve to give an overall impression of the effect of HDL-C at increasing levels of LDL-C.

Conclusions

HDL-C levels are related to the risk of new cardiovascular events in patients with clinically manifest vascular disease treated with usual dose lipid-lowering therapy but not in patients treated with intensive lipid-lowering medication, irrespective of LDL-C.

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Reprint requests and correspondence: Dr. Frank L. J. Visseren, Department of Vascular Medicine, University Medical Center Utrecht, P.O. Box 85500, 3508 GA Utrecht, the Netherlands. E-mail: F.L.J.Visseren@umcutrecht.nl.

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Key Words: HDL cholesterol ■ LDL cholesterol ■ secondary prevention ■ statins.

APPENDIX

For supplemental tables, please see the online version of this article.