

# Low-Density Lipoprotein Cholesterol, Non-High-Density Lipoprotein Cholesterol, Triglycerides, and Apolipoprotein B and Cardiovascular Risk in Patients With Manifest Arterial Disease



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Low-density lipoprotein cholesterol (LDL-C) only partly represents the atherogenic lipid burden, and a growing body of evidence suggests that non-high-density lipoprotein cholesterol (non-HDL-C), triglycerides, and apolipoprotein B (apoB) are more accurate in estimating lipid-related cardiovascular disease risk. Our objective was to compare the relation among LDL-C, non-HDL-C, triglycerides, and apoB and the occurrence of future vascular events and mortality in patients with manifest arterial disease. This is a prospective cohort study of 7,216 patients with clinically manifest arterial disease in the Secondary Manifestations of Arterial Disease Study. Cox proportional hazard models were used to quantify the risk of major cardiovascular events (MACE; i.e., stroke, myocardial infarction, and vascular mortality) and all-cause mortality. Interaction was tested for type of vascular disease at inclusion. MACE occurred in 1,185 subjects during a median follow-up of 6.5 years (interquartile range 3.4 to 9.9 years). Adjusted hazard ratios (HRs) of MACE per 1 SD higher were for LDL-C (HR 1.15, 95% confidence interval [CI] 1.09 to 1.22), for non-HDL-C (HR 1.17, 95% CI 1.11 to 1.23), for log(triglycerides) (HR 1.12, 95% CI 1.06 to 1.19), and for apoB HR (1.12, 95% CI 0.99 to 1.28). The relation among LDL-C, non-HDL-C, and cardiovascular events was comparable in patients with cerebrovascular disease, coronary artery disease, or polyvascular disease and absent in those with aneurysm of abdominal aorta or peripheral artery disease. In conclusion, in patients with a history of cerebrovascular, coronary artery, or polyvascular disease, but not aneurysm of abdominal aorta or peripheral artery disease, higher levels of LDL-C and non-HDL-C are related to increased risk of future MACE and of comparable magnitude. © 2016 Elsevier Inc. All rights reserved. (Am J Cardiol 2016;118:804–810)

Several studies have made a direct comparison to assess which lipid parameters have the strongest relation with risk of vascular disease and overall; apolipoprotein B (apoB) and non-high-density lipoprotein cholesterol (non-HDL-C) appear to be favorable over low-density lipoprotein cholesterol (LDL-C).<sup>1–5</sup> Triglyceride-rich remnants are also strongly related to cardiovascular events and triglycerides and, therefore, could also be a good marker.<sup>6</sup> Most studies<sup>1–5,7,8</sup> comparing lipid parameters to cardiovascular events were done in a primary prevention setting, whereas patients at highest risk of cardiovascular events are those with a history of clinically manifest arterial disease. Few studies included patients with coronary heart disease, but these studies were all randomized controlled trials with statins.<sup>9,10</sup> In these studies, non-HDL-C also had a stronger

association with risk of recurrent coronary or cerebral ischemic events, although point estimates were lower for recurrent compared with first major cardiovascular events (MACE). Because type of vascular disease (coronary, cerebrovascular, and peripheral artery) influences the risk of future vascular events,<sup>11</sup> there is some evidence to assume that type or extent of atherosclerosis can also influence the relation between lipids and risk of a recurrent cardiovascular disease. The aim of this study, therefore, was to evaluate and compare the relation between LDL-C, non-HDL-C, triglycerides, and apoB and the occurrence of future vascular events and mortality, in patients with clinically manifest arterial disease, and whether location of vascular disease influences this relation.

## Methods

Data were used from patients enrolled in the Second Manifestations of Arterial Disease (SMART) cohort. This is a prospective, ongoing cohort study at the University Medical Center Utrecht, The Netherlands, designed to study the presence of concomitant arterial disease and risk factors for atherosclerosis in a high-risk population. Patients, aged 18 to 80 years, newly referred to our institution with clinically manifest arterial disease or with a vascular risk factor,

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See page 809 for disclosure information.

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hyperlipidemia, hypertension, or diabetes mellitus (types 1 and 2) were asked to participate. The study was approved by the medical ethics committee of the University Medical Center Utrecht, and informed consent was obtained from all patients ( $n = 10,645$ ). A detailed description regarding study rationale and design has been published before.<sup>12</sup> The present study used data from 7,216 patients enrolled from September 1996 to March 2014 with either a history or a recent diagnosis of manifest arterial disease. From 2005 onward, apoB was measured, and since 2006, apoB became part of the standard screening protocol; therefore, ApoB levels were available in 3,503 patients.

Clinically manifest atherosclerotic arterial disease was defined as cerebral, coronary, or peripheral artery disease or aneurysm of the abdominal aorta. Cerebrovascular disease included transient ischemic attack, cerebral infarction, amaurosis fugax, retinal infarction, or a history of carotid surgery. Coronary artery disease was defined as angina pectoris, myocardial infarction, cardiac arrest, or coronary revascularization (coronary bypass surgical procedure or coronary angioplasty). Patients with peripheral artery disease had symptomatic and documented obstruction of an artery in a distal extremity and underwent surgical operation (percutaneous transluminal angioplasty, bypass, or amputation). Abdominal aortic aneurysm (suprarenal or infrarenal) was defined as a diameter of  $>3$  cm or a history of aortic aneurysm surgery. When patients had vascular disease at multiple locations, they were defined as having polyvascular disease. At inclusion, all patients completed a health questionnaire and responded to questions including history of vascular disease, hypertension, diabetes mellitus, current medication use, and lifestyle. A physical examination took place where height, weight, and blood pressure was measured. Blood samples were collected at baseline after an overnight fast. Plasma total cholesterol, triglycerides, and HDL-C were measured using commercial enzymatic dry chemistry kits (Johnson & Johnson, New Brunswick and Boehringer-Mannheim, Mannheim, Germany, respectively). LDL-C was calculated using the Friedewald formula<sup>13</sup> up to a plasma triglycerides level of 9 mmol/L. This is in line with data showing that the Friedewald formula can be used up to this level.<sup>14</sup> In 32 patients, plasma triglycerides levels were  $>9$  mmol/L and LDL-C could not be calculated. Non-HDL-C was calculated as total cholesterol minus HDL-C and apoB was measured on a BNII nephelometer (Siemens, Erlangen, Germany).

Patients were biannually asked to fill in a short questionnaire regarding hospitalization and outpatient clinic visits. If a patient reported a possible event, all available relevant data were collected, and the SMART Endpoint Committee that consisted of 3 staff members independently classified all events. Outcomes of interest for this study were occurrence of stroke (ischemic and hemorrhagic, fatal, and nonfatal), myocardial infarction (fatal and nonfatal), cardiovascular mortality (fatal stroke, fatal myocardial infarction, death due to terminal heart failure, ruptured abdominal aortic aneurysm, and sudden death), MACE (composite of any of the previously listed outcomes), and all-cause mortality. Follow-up duration was defined as the period between study enrollment and first recurrent vascular event or death from any cause, date to loss of follow-up, or the preselected date of March 2014.

Baseline characteristics of the total study population are presented for the total study population and stratified according to the location of vascular disease. Single imputation methods were used to account for missing data (which was 2.2% for LDL-C, 0.7% for non-HDL-C, 0.6% for triglycerides, alcohol, and smoking status, and 0.2% for body mass index [BMI]). Because apoB was one of the determinants and not missing at random, we choose not to impute these values. If a patient had multiple events, the first recorded event was used in the analyses and patients were censored if they were lost to follow-up. Cox proportional hazard models were used to calculate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) per lipid parameter for the occurrence of stroke, myocardial infarction, cardiovascular mortality, MACE, and all-cause mortality. Two models were used: model I with adjustment for age and gender and model II with adjustment for age, gender, BMI, smoking, alcohol, and diabetes mellitus. Because triglycerides levels had a skewed distribution, log transformation was applied, and to be able to compare effect sizes of lipid parameters, HR were calculated per 1 standard deviation (1 SD) increase in LDL-C, non-HDL-C,  $\log(\text{triglycerides})$ , and ApoB. A sensitivity analysis took place with additional adjustment for lipid-lowering therapy.

ApoB was not measured in the total population, and therefore, analyses were repeated in a subset of patients with complete lipid measurements ( $n = 3,492$ ). Effect modification on a multiplicative scale was tested by adding an interaction term between “LDL-C/1 SD, non-HDL-C/1 SD, and  $\log(\text{triglycerides})/1 \text{ SD} \times \text{type of vascular disease}$ .” The models with and without the interaction term were compared using the likelihood ratio test, and a  $p$  value  $<0.05$  was considered statistically significant. If interaction was present, analyses were stratified per type of vascular disease (cerebrovascular disease, coronary artery disease, abdominal aortic aneurysm, peripheral artery disease, or polyvascular disease). This could not be done for apoB because of a limited number of events in the subsets. Effect modification was also tested for diabetes mellitus, age  $\geq 65$  versus  $<65$  years, number of beds with vascular disease, categorized as 1, 2, or  $>2$ , year of inclusion, categorized into 4 equal groups, and lipid parameters for risk of MACE. Next, risk of vascular events and/or mortality was also calculated per quartile of each of the lipid parameters, using the lowest quartile as reference. The quartile ranges of LDL-C were  $<2.12$ , 2.12 to 2.73, 2.74 to 3.53, and  $>3.53$  mmol/L, for non-HDL-C were  $<2.75$ , 2.75 to 3.48, 3.47 to 4.38, and  $>4.38$  mmol/L, for triglycerides were  $<1.00$ , 1.00 to 1.41, 1.40 to 2.00 mmol/L, and  $>2.00$ , and for apoB, quartiles were divided into  $<0.68$ , 0.68 to 0.81, 0.82 to 0.99, and  $>0.99$  g/dl. The proportional hazards assumptions were verified using Schoenfeld residuals plotted against (age adjusted) time scale. The open source software program R 3.2.0 (R Development Core Team, Vienna, Austria) was used for data analyses.

## Results

The mean age at baseline was  $60 \pm 10$  years, and 74% were men. Patients with coronary artery disease on average

Table 1  
Patient characteristics of the study population according to location of vascular disease at baseline

Variable	Total Study Population (n = 7216)	Cerebrovascular Disease* (n = 1549)	Coronary Artery Disease (n = 3464)	Aneurysm of Abdominal Aorta (n = 265)	Peripheral Artery Disease (n = 825)	Polyvascular Disease (n = 1113)
Age (years)	60.1 (10.3)	58.1 (11.4)	60.0 (9.6)	65.0 (10.3)	57.6 (10.7)	63.5 (9.2)
Male sex	5319 (74%)	895 (58%)	2800 (81%)	226 (85%)	514 (62%)	884 (79%)
Current smoking	2300 (32%)	524 (34%)	799 (23%)	99 (37%)	499 (60%)	379 (34%)
Current alcohol use	793 (11%)	182 (12%)	332 (10%)	35 (13%)	71 (9%)	173 (16%)
Hypertension	6217 (86%)	1128 (73%)	3288 (95%)	208 (78%)	580 (70%)	1013 (91%)
Diabetes mellitus	1259 (17%)	203 (13%)	624 (18%)	33 (12%)	138 (17%)	261 (23%)
Cerebrovascular disease	2120 (29%)	1549 (100%)	-	-	-	571 (51%)
Coronary Artery disease	4365 (60%)	-	3464 (100%)	-	-	901 (81%)
Aneurysm of abdominal aorta	624 (9%)	-	-	265 (100%)	-	359 (32%)
Peripheral vascular disease	1373 (19%)	-	-	-	825 (100%)	548 (49%)
Blood pressure lowering agents	5315 (74%)	810 (52%)	3157 (91%)	138 (52%)	319 (39%)	891 (80%)
Statin therapy	4776 (66%)	823 (53%)	2794 (81%)	85 (32%)	306 (37%)	768 (69%)
Anti-platelet / anti-coagulant agents	5964 (83%)	1215 (78%)	3210 (93%)	105 (40%)	436 (53%)	998 (90%)
Body mass index (kg/m <sup>2</sup> )	26.8 (4.0)	26.4 (4.2)	27.3 (3.8)	26.0 (3.7)	26.0 (4.4)	26.9 (3.9)
Systolic blood pressure (mmHg)	140 (21)	142 (22)	137 (20)	144 (20)	145 (21)	144 (21)
Diastolic blood pressure (mmHg)	81 (11)	83 (12)	80 (11)	85 (12)	82 (11)	80 (12)
Total cholesterol (mmol/l)	4.86 (1.21)	5.00 (1.20)	4.58 (1.12)	5.41 (1.31)	5.56 (1.21)	4.91 (1.17)
Triglycerides (mmol/l)	1.4 (1.0 - 2.0)	1.3 (0.9 - 1.8)	1.4 (1.0 - 1.9)	1.4 (1.1 - 2.0)	1.5 (1.1 - 2.2)	1.6 (1.1 - 2.3)
High-density lipoprotein cholesterol (mmol/l)	1.23 (0.37)	1.34 (0.42)	1.19 (0.32)	1.22 (0.39)	1.28 (0.41)	1.17 (0.35)
Low-density lipoprotein cholesterol (mmol/l)	2.87 (1.04)	2.97 (1.07)	2.64 (0.93)	3.42 (1.16)	3.44 (1.10)	2.90 (1.03)
Non-high-density lipoprotein cholesterol (mmol/l)	3.63 (1.21)	3.65 (1.21)	3.39 (1.12)	4.20 (1.33)	4.29 (1.26)	3.74 (1.17)
Apolipoprotein B (g/dl) <sup>†</sup>	0.84 (0.24)	0.84 (0.27)	0.83 (0.23)	0.93 (0.27)	0.94 (0.26)	0.84 (0.23)
High-sensitivity C-reactive protein (mg/L)	2.0 (1.0 - 4.4)	1.8 (0.8 - 4.1)	1.6 (0.8 - 3.4)	3.7 (1.6 - 7.6)	3.2 (1.5 - 6.1)	2.9 (1.4 - 5.8)

All data are displayed as mean  $\pm$  SD, median (interquartile range) or n (%).

\* Cerebrovascular disease was caused by hemorrhagic stroke in 17 of the 1549 patients.

<sup>†</sup> Apolipoprotein B measurements were available in a subset of n = 3503 patients.

were more often diagnosed with hypertension, were more likely to use blood pressure-lowering medication, statins and antiplatelet or anticoagulant therapy, and had a higher BMI compared with the total study population. Patients with peripheral artery disease more often were current smokers. In 87% of the patients with polyvascular disease, vascular disease was present in 2 vascular beds and 12% had vascular disease in 3 locations. Patients with abdominal aortic aneurysm and polyvascular disease were on average older at baseline and those with polyvascular disease were more likely to be diagnosed with diabetes and those with peripheral artery disease or abdominal aortic aneurysm had on average higher total cholesterol, LDL-C, non-HDL-C, and apoB levels (Table 1).

During a median follow-up of 6.5 years (IQR 3.4 to 9.9 years), 1,324 patients (18%) died (of whom 692 from a vascular cause); 330 patients (5%) had a stroke, 435 patients (6%) had a myocardial infarction, and 1,185 patients (16%) had the composite outcome, MACE. After adjustment for confounding, 1 SD higher LDL-C, non-HDL-C, triglycerides, and apoB were related with higher risk of MACE (HR 1.15, 95% CI 1.09 to 1.22 for LDL-C; HR 1.17, 95% CI 1.11 to 1.23 for non-HDL-C; HR 1.12, 95% CI 1.06 to 1.19 for log(triglycerides); and HR 1.12, 95% CI 0.99 to 1.27 for apoB) and also with increased risk of all-cause mortality, as presented in Figure 1 (and in Supplementary Table 1, which can be found online only). Although CIs of apoB were wide, the risk of myocardial infarction was 23% higher per 1 SD higher apoB. In the sensitivity analysis

with additional adjustment for lipid-lowering therapy, the effect estimates did not change, nor did additional adjustment for hypertension, use of antiplatelet/anticoagulant agents, and hs-CRP. Because apoB was measured from 2005 onward, we repeated the analyses in a subset of patients (n = 3,492) with complete lipid measurements (baseline characteristics are provided in Supplementary Table 2, which can be found online only). Point estimates for risk of vascular events and mortality for LDL-C, non-HDL-C, and apoB in the subset were comparable with the total study population (Supplementary Figure 1 and in Supplementary Table 1, which can be found online only). The relation between log(triglycerides) and cardiovascular endpoints, however, was less evident in the subset of patients with complete lipid measurements.

The relation between levels of triglycerides and risk of MACE was dependent of location of vascular disease at inclusion (p value = 0.04 for interaction between log(triglycerides)  $\times$  type of vascular disease). For LDL-C and non-HDL-C, interaction was not statistically significant (p values 0.66 and 0.58, respectively). Results stratified according to the type of vascular disease at baseline are presented in Table 2. After adjustment for confounding, 1 SD higher LDL-C and non-HDL-C were related to an increased risk of MACE in patients with a history of cerebrovascular disease, coronary artery disease, or polyvascular disease. The effect of 1 SD higher triglycerides on risk of MACE was comparable magnitude in patients with cerebrovascular disease or coronary artery disease but

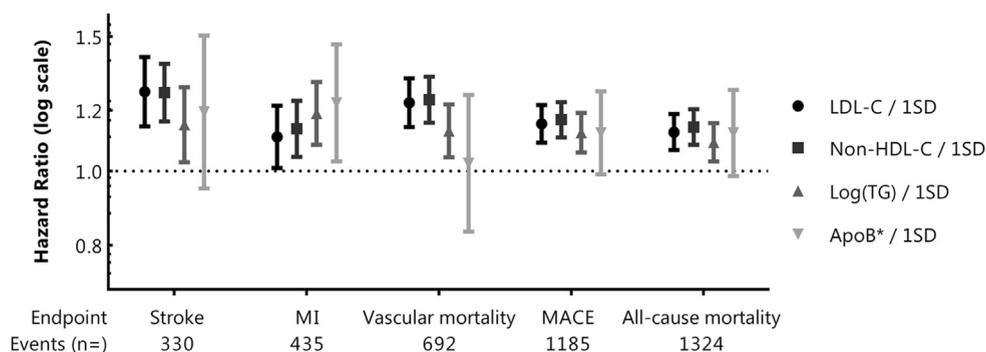


Figure 1. The relation between lipid measurements and cardiovascular events and mortality. Presented data are HRs with 95% CI, adjusted for age, gender, BMI, smoking, alcohol, and diabetes mellitus. 1 SD of LDL-C = 1.05 mmol/L, non-HDL-C = 1.21 mmol/L, log(TG) = 0.53 mmol/L; in the total study population of  $n = 7,216$  and 1 SD of apoB = 0.24 g/L, measured in  $n = 3,503$  patients. \* ApoB measurements were available in a subset 3,503 patients. Exact HRs are presented in [Supplementary Table 1](#).

Table 2

The relation between low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, log transformed triglycerides per 1 standard deviation and risk of major cardiovascular events stratified for location of vascular disease

Subset	Size (n =)	Events (n =)	LDL-C/1 SD	Non-HDL-D/1 SD	Log(TG)/1 SD*
			HR (95% CI)	HR (95% CI)	HR (95% CI)
Cerebrovascular disease	1549	216	1.16 (1.01 - 1.33)	1.20 (1.05 - 1.37)	1.15 (1.00 - 1.32)
Coronary artery disease	3455	410	1.14 (1.04 - 1.25)	1.14 (1.05 - 1.23)	1.10 (1.00 - 1.22)
Peripheral artery disease	825	134	1.00 (0.84 - 1.20)	1.07 (0.90 - 1.28)	1.12 (0.94 - 1.33)
Aneurysm of abdominal aorta	265	74	1.10 (0.85 - 1.44)	1.07 (0.82 - 1.39)	0.92 (0.70 - 1.20)
Polyvascular disease	1113	344	1.13 (1.02 - 1.26)	1.12 (1.00 - 1.25)	1.06 (0.95 - 1.19)

Presented data are Hazard ratio with 95% confidence intervals (HR (95% CI)), adjusted for age, sex, BMI, smoking, alcohol and diabetes mellitus.

LDL-C = low-density lipoprotein-cholesterol; log(TG) = log-transformed triglycerides; MACE = major cardiovascular events; MI = myocardial infarction; non-HDL-C = non-high-density lipoprotein-cholesterol.

\* P value of 0.04 for interaction between log(TG)/1 standard deviation and type of vascular disease.

nonsignificant in those with polyvascular disease. In patients with a history of peripheral artery disease or abdominal aortic aneurysm, no association was present between lipid parameters and risk of MACE. No interaction was present between diabetes mellitus and LDL-C (p value 0.88), non-HDL-C (p value 0.58), log(triglycerides) (p value 0.85), or apoB (p value 0.83) and the risk of future MACE. Interaction was also absent for age  $\geq 65$  versus  $< 65$  years (p values were 0.07, 0.11, 0.99, and 0.81, respectively), for number of beds with vascular disease (p values 0.31, 0.92, 0.10, and 0.52, respectively), and for year of inclusion (p value 0.08, 0.15, 0.90, and 0.38, respectively)  $\times$  lipid parameters on risk of MACE.

The risk of cardiovascular mortality, MACE, and all-cause mortality was higher across quartiles of LDL-C, non-HDL-C, and triglycerides (Figure 2). Patients in the top quartile of non-HDL-C had an HR of 2.09 (95% CI 1.62 to 2.69) compared with the lowest quartile for risk of vascular mortality, HR 1.60 (95% CI 1.34 to 1.91) for risk of future MACE, and HR 1.54 (95% CI 1.29 to 1.83) for risk of all-cause mortality. The relation between LDL-C or triglycerides and future MACE were less strong; HR for LDL-C was 1.47 (95% CI 1.24 to 1.75) and for triglycerides 1.32 (95% CI 1.11 to 1.57) and were also lower for risk of all-cause mortality; HR for LDL-C was 1.38 (95% CI 1.16 to 1.63) and for triglycerides was 1.19 (95% CI 1.00 to 1.40). Patients in the top quartile of LDL-C ( $> 3.53$  mmol/L)

had the highest risk for future stroke (HR of 1.88; 95% CI 1.33 to 2.64) compared with those in the lowest quartile (LDL-C  $< 2.12$  mmol/L). Risk of future myocardial infarction was highest for patients in the top quartile of triglycerides ( $> 2.00$  mmol/L) with an HR of 1.63 (95% CI 1.20 to 2.21) and for patients in the top quartile of non-HDL-C (HR 1.55; 95% CI 1.15 to 2.08). None of the apoB quartiles were associated with any of the end points compared with the lowest quartile.

## Discussion

In this study with patients from a secondary prevention cohort, higher levels of LDL-C and non-HDL-C, triglycerides, and apoB are related to increased risk of future MACE. However, after stratification for type of vascular disease, the relation between higher levels of LDL-C and non-HDL-C and risk of MACE are only present in patients with cerebrovascular, coronary artery, or polyvascular disease and absent in patients with abdominal aortic aneurysm or peripheral artery disease. Higher levels of triglycerides were also related to increased risk of MACE in patients with cerebrovascular disease or coronary artery disease.

The results of this present study are in line with a meta-analysis of individual patient data from randomized controlled trials with statin therapy,<sup>10</sup> where in 24,053

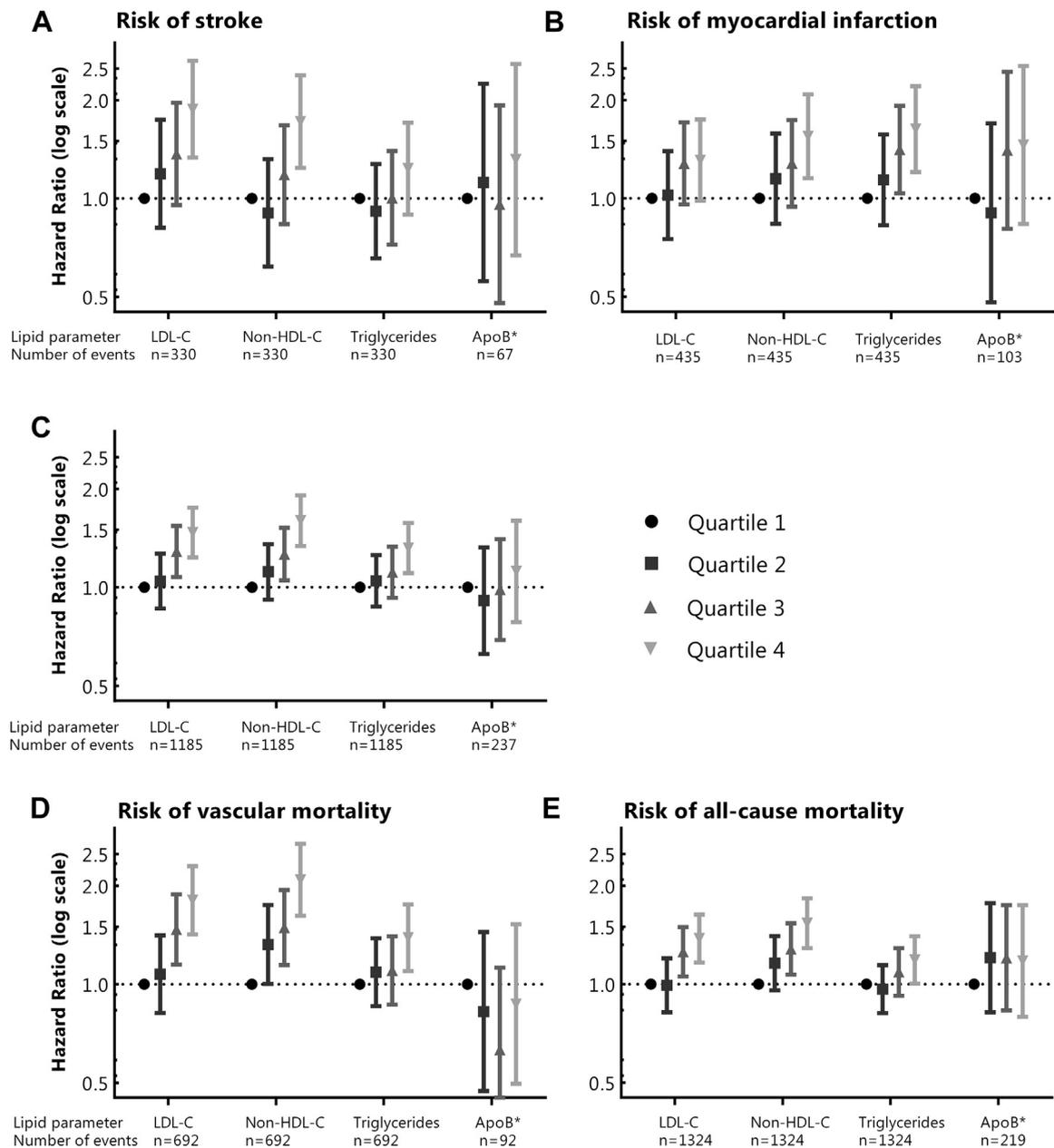


Figure 2. Risk of vascular events and mortality, according to quartiles of LDL-C, non-HDL-C, log-transformed triglycerides, and apoB, using the lowest quartile as reference. Presented data are HRs with 95% confidence interval of lipid quartiles, using the lowest quartile as reference, for risk of stroke (A), myocardial infarction (B), MACEs (C), vascular mortality (D), and all-cause mortality (E). HRs are adjusted for age, gender, BMI, smoking, alcohol, and diabetes mellitus. The range of LDL-C quartiles were <2.12, 2.12 to 2.73, 2.74 to 3.53, and >3.53 mmol/L, the range of non-HDL-C quartiles were <2.75, 2.75 to 3.47, 3.48 to 4.38, and >4.38 mmol/L, for TG quartiles, the range was <1.00, 1.00 to 1.40, 1.41 to 2.00, and >2.00 mmol/L; and for apoB, quartiles were divided into <0.68, 0.68 to 0.81, 0.82 to 0.99, and >0.99 g/dl. \* ApoB measurements were available in a subset of 3,503 patients.

patients with prevalent CHD, comparable adjusted HR for MACE per 1 SD higher LDL-C, non-HDL-C, and apoB were found. However, there are also studies showing that non-HDL-C and/or apoB are more strongly related to cardiovascular events than LDL-C.<sup>5,15,16</sup> A possible explanation could be a difference in endpoint because most studies focused on coronary heart disease as an endpoint instead of MACE that also includes nonfatal stroke.<sup>1,3-5</sup> In our study, apoB was not associated with an increased risk MACE. A possible explanation could be that the patients in whom apoB was measured

were more recently included and, therefore, probably received better (preventative) care. Statins, for instance, were prescribed more often and LDL-C levels were lower in these patients compared with the total study population. Interestingly, apoB was stronger related with the risk of myocardial infarction, compared with LDL-C, non-HDL-C, and triglycerides. A possible explanation could be that because apoB has a stronger association with inflammation and insulin resistance<sup>17</sup> and because inflammation plays an important role in the pathogenesis of myocardial infarction, apoB has a

stronger association with risk of myocardial infarction than the other lipid parameters.

Another explanation for the difference in findings could be differences in study populations. Most observational studies that compare lipids included patients free of cardiovascular disease at baseline,<sup>1–5</sup> whereas the present study population consisted of patients with a variety of atherosclerotic disease. We hypothesized that type of vascular disease would influence the association between lipids and risk of recurrent events and that in patients with extensive atherosclerosis, that is, multiple arterial events, the risk attributable to lipids would be low or even negligible because these patients already have a very high absolute risk of MACE. Supporting this hypothesis is a recent study regarding the association between type 2 diabetes and risk of recurrent MACE, which showed that type 2 diabetes was no longer a risk factor for recurrent MACE in patients with vascular disease at multiple locations.<sup>18</sup> In our study, we found that point estimates for the association between non-HDL-C, less so for LDL-C and risk of MACE, were lower in patients with polyvascular disease than in the total study population, thus not supporting our hypothesis. The risk of recurrent MACE per 1 SD higher LDL-C, non-HDL-C, and triglycerides was comparable in patients with a history of cerebrovascular disease or coronary artery disease to the total study population. In patients with a history of abdominal aortic aneurysm or peripheral artery disease, no association was found between lipids and vascular risk and an explanation could be limited power or the difference in risk factor profile. Possibly other risk factors than lipids, such as smoking, high blood pressure, and age drive risk of recurrent MACE in patients with abdominal aortic aneurysm or peripheral artery disease and adjusting for smoking, age, and other factors attenuated the relation between lipids and recurrent vascular events.

Compared with LDL-C, non-HDL-C, triglycerides, or apoB overall did not performed vastly better in estimating risk of recurrent events in our study. Although the body of evidence is growing in favor of apoB and non-HDL-C, using LDL-C as the main lipid parameter in clinical practice appears justifiable in patients with atherosclerotic disease. Measurement of triglycerides, non-HDL-C, and apoB, however, remains important, especially in diagnosing specific dyslipidemias, such as familial hypercholesterolemia and dysbetalipoproteinemia, because these patients and their families are at even higher risk of cardiovascular events.<sup>19</sup>

The strengths of this study are the prospective design and relatively large sample size. The SMART cohort is a contemporary hospital-based cohort with low loss to follow-up (6%) and a large number of clinical events. To appreciate the findings, limitations also need to be addressed. First, our cohort represents a West European population with predominately Caucasians, which may not be representative of other geographical locations. Second, measurement of apoB became part of the standard baseline screening in 2006 and, therefore, was available in 49% of the total study population. Although CIs were wide, point estimates were consistent in patients with complete lipid measurements and because of the recent date of inclusion, perhaps give a better reflection of the present clinical situation. Because of a limited number of events, however, stratification for type of

vascular disease at inclusion was not possible in the analyses with apoB. Third, LDL-C was not measured directly but calculated using the Friedewald formula, up to a serum triglycerides level of 9 mmol/L, instead of the usual 4.5 mmol/L. Previous studies have found a linear relation and high correlation between fasting direct measurement of LDL-C and calculated LDL-C using the Friedewald formula. In our study population, 3% of the patients had a triglycerides >4.5 mmol/L. In these patients, LDL-C values calculated with the Friedewald formula might be underestimated, which could have led to an underestimation in the relation between LDL-C per 1 SD and risk of MACE.

A fourth limitation is that plasma lipid levels and data regarding possible confounders, such as lipid-lowering therapy, were only present at baseline. Although a sensitivity analysis with additional adjustment of lipid-lowering therapy did not change the results, risk of bias due to preferential use of statins in high-risk subjects as showed recently by Colantonio et al<sup>20</sup> is still present. Besides, since the start of the study in 1996 and present day, secondary prevention and treatment options for cardiovascular events have changed and also might have influenced the association between lipids and cardiovascular disease risk. Interaction between year of inclusion  $\times$  lipid parameters and risk of cardiovascular events, however, was not present.

In this study, higher levels of LDL-C and non-HDL-C are related to an increased risk of MACE in patients with cerebrovascular, coronary artery, or polyvascular disease and absent in patients with abdominal aortic aneurysm or peripheral artery disease.

**Acknowledgment:** We gratefully acknowledge the contribution of the SMART research nurses, R. van Petersen (data manager), B.G.F. van Dinther (manager SMART study and Utrecht Cardiovascular Cohort), and the members of the SMART study group: A. Algra, MD, PhD; Dr. van der Graaf; D. E. Grobbee, MD, PhD; and G. E. H. M. Rutten, MD, PhD, Julius Center for Health Sciences and Primary Care; Dr. Visseren, Department of Internal Medicine; Dr. de Borst, Department of Vascular Surgery; Dr. Kappelle, Department of Neurology; T. Leiner, MD, PhD, Department of Radiology; and Dr. Nathoe, Department of Cardiology.

#### Disclosures

The authors have no conflicts of interest to disclose.

#### Supplementary Data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.amjcard.2016.06.048>.

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