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High-density lipoprotein cholesterol, coronary artery disease, and cardiovascular mortality

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Abstract: AIMS: High-density lipoprotein (HDL) cholesterol is a strong predictor of cardiovascular mortality. This work aimed to investigate whether the presence of coronary artery disease (CAD) impacts on its predictive value. METHODS AND RESULTS: We studied 3141 participants (2191 males, 950 females) of the LUdwigshafen RIsk and Cardiovascular health (LURIC) study. They had a mean ± standard deviation age of 62.6 ± 10.6 years, body mass index of 27.5 ± 4.1 kg/msup2;, and HDL cholesterol of 38.9 ± 10.8 mg/dL. The cohort consisted of 699 people without CAD, 1515 patients with stable CAD, and 927 patients with unstable CAD. The participants were prospectively followed for cardiovascular mortality over a median (inter-quartile range) period of 9.9 (8.7-10.7) years. A total of 590 participants died from cardiovascular diseases. High-density lipoprotein cholesterol by tertiles was inversely related to cardiovascular mortality in the entire cohort (P = 0.009). There was significant interaction between HDL cholesterol and CAD in predicting the outcome (P = 0.007). In stratified analyses, HDL cholesterol was strongly associated with cardiovascular mortality in people without CAD [3rd vs. 1st tertile: HR (95% CI) = 0.37 (0.18-0.74), P = 0.005], but not in patients with stable [3rd vs. 1st tertile: HR (95% CI) = 0.81 (0.61-1.09), P = 0.159] and unstable [3rd vs. 1st tertile: HR (95% CI) = 0.91 (0.59-1.41), P = 0.675] CAD. These results were replicated by analyses in 3413 participants of the AtheroGene cohort and 5738 participants of the ESTHER cohort, and by a meta-analysis comprising all three cohorts. CONCLUSION: The inverse relationship of HDL cholesterol with cardiovascular mortality is weakened in patients with CAD. The usefulness of considering HDL cholesterol for cardiovascular risk stratification seems limited in such patients.

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High Density Lipoprotein Cholesterol, Coronary Artery Disease, and Cardiovascular Mortality

Brief title: **HDL Cholesterol in Cardiovascular Disease**

Guenther Silbernagel, MD[1], Ben Schöttker, PHD[2], Sebastian Appelbaum[3], Hubert Scharnagl, PHD[4], Marcus E. Kleber, PHD[5], Tanja B. Grammer, MD[5], Andreas Ritsch, PHD[6], Ute Mons, PHD[2], Bernd Holleczek[2, 7], Georg Goliasch, MD/PHD[8], Alexander Niessner, MD/Msc[8], Bernhard O. Boehm, MD[9, 10], Renate B. Schnabel, MD[3], Hermann Brenner, MD[2], Stefan Blankenberg, MD[3], Ulf Landmesser, MD[11], Winfried März, MD[4, 5, 12]

[1]Department of Angiology, Swiss Cardiovascular Center, Inselspital, University of Bern, Switzerland
[2]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany
[3]Department of Cardiology, University Heart Center Hamburg, Germany
[4]Clinical Institute of Medical and Chemical Laboratory Diagnostics, Graz Medical University, Austria
[5]Institute of Public Health, Social and Preventive Medicine, Mannheim Medical Faculty, University of Heidelberg, Mannheim, Germany
[6]Division of Angiology, Department of Internal Medicine, Innsbruck Medical University, Austria
[7]Saarland Cancer Registry, Saarbrücken, Germany
[8]Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Austria
[9]Division of Endocrinology and Diabetes, Department of Internal Medicine, Ulm University, Germany
[10]Lee Kong Chian School of Medicine, Nanyang Technological University and Imperial College London, Singapore
[11]Division of Cardiology, Department of Internal Medicine, University of Zürich, Switzerland
[12]Synlab Services GmbH, Synlab Academy, Mannheim, Germany

* **Address correspondence to:**
Dr. Guenther Silbernagel
Department of Angiology, Swiss Cardiovascular Center, Inselspital, University of Bern, 3010 Bern, Switzerland
Tel.: +41 31 632 3034
Fax: +41 31 632 4793
E-mail: guenther.silbernagel@insel.ch

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Abstract

Aims: High-density lipoprotein (HDL) cholesterol is a strong predictor of cardiovascular mortality. This work aimed to investigate, whether the presence of coronary artery disease (CAD) impacts on its predictive value.

Methods and Results: We studied 3,141 participants (2,191 males, 950 females) of the LUdwigshafen RIsk and Cardiovascular health study. They had a mean±standard deviation age of 62.6±10.6 years, body mass index of 27.5±4.1 kg/m², and HDL cholesterol of 38.9±10.8 mg/dl. The cohort consisted of 699 people without CAD, 1,515 patients with stable CAD, and 927 patients with unstable CAD. The participants were prospectively followed for cardiovascular mortality over a median (interquartile range) period of 9.9 (8.7-10.7) years. A total of 590 participants died from cardiovascular diseases. HDL cholesterol by tertiles was inversely related to cardiovascular mortality in the entire cohort (p=0.009). There was significant interaction between HDL cholesterol and CAD in predicting the outcome (p=0.007). In stratified analyses, HDL cholesterol was strongly associated with cardiovascular mortality in people without CAD (3^{rd} vs. 1^{st} tertile: HR(95%CI)=0.37 (0.18-0.74), p=0.005), but not in patients with stable (3^{rd} vs. 1^{st} tertile: HR(95%CI)=0.81 (0.61-1.09), p=0.159) and unstable (3^{rd} vs. 1^{st} tertile: HR(95%CI)=0.91 (0.59-1.41), p=0.675) CAD. These results were replicated by analyses in 3,413 participants of the Athero*Gene* cohort and 5,738 participants of the ESTHER cohort, and by a meta-analysis comprising all three cohorts.

Conclusion: The inverse relationship of HDL cholesterol with cardiovascular mortality is weakened in patients with CAD. The usefulness of considering HDL cholesterol for cardiovascular risk stratification seems limited in such patients.

Key words: High density lipoprotein cholesterol, atherosclerosis, cardiovascular mortality

Introduction

Epidemiologic data have provided broad evidence that low concentrations of high-density lipoprotein (HDL) cholesterol indicate increased cardiovascular risk (1-4). Although less consistently (5), this relationship is even apparent in patients treated with statins (6). Therefore, raising HDL cholesterol has become a therapeutic target in coronary artery disease (CAD) (7).

Inhibition of cholesterol-ester transfer protein (CETP) is associated with a substantial increase of HDL cholesterol (8-12). Nevertheless, the use of torcetrapib did not improve but rather worsened prognosis in the ILLUMINATE trial (11). Treatment with dalcetrapib did not reduce the risk of cardiovascular events in the recently published dal-OUTCOMES trial either (12). These disappointing results may in part be attributed to off-target effects of cholesterol ester transfer protein (CETP) inhibitors, most importantly an increase in systolic blood pressure and pro-inflammatory activity (11, 12). An alternative explanation would be that raising HDL cholesterol is less beneficial in certain subgroups, for example in patients with CAD. Notably, ILLUMINATE included patients at high cardiovascular risk and all participants of the dal-OUTCOMES trial had suffered a recent acute coronary syndrome (11. 12).

Therefore, the aim of the present study was to investigate, whether CAD at baseline affects the prognostic value of HDL cholesterol for cardiovascular mortality. The exploratory analyses were performed in the **"**LUdwigshafen RIsk and Cardiovascular health" (LURIC) cohort (13, 14). Replication of the findings obtained from LURIC was sought in the Athero*Gene* (15, 16) and the ESTHER (17, 18) cohorts. Considering that their clinical presentation, treatment, and prognosis differ markedly, stable and unstable CAD were analyzed separately.

Methods

Study design, participants and clinical characterization

LURIC

A total of 3,316 patients, who were referred for coronary angiography to the Ludwigshafen Heart Center in South-West Germany, were recruited between July 1997 and January 2000 (13). Inclusion criteria were: German ancestry, clinical stability except for acute coronary syndromes, and the availability of a coronary angiogram. The indications for angiography in individuals in clinically stable condition were chest pain and/or noninvasive test results consistent with myocardial ischemia. Individuals suffering from any acute illness other than acute coronary syndromes, chronic non-cardiac diseases, or malignancy within the five past years, and those unable to understand the purpose of the study were excluded. Subjects with missing information on the clinical presentation of CAD, missing laboratory measurements or missing information on the cause of death were additionally ruled out resulting in a subgroup of 3,141 participants for the present analyses. *CAD* was diagnosed if coronary angiography revealed stenosis of one or more vessels ≥20%. Unstable angina was diagnosed according to Braunwald (13). Acute myocardial infarction was defined as a myocardial infarction that had occurred within the four weeks prior to enrolment into LURIC. A definite ST-elevation myocardial infarction was diagnosed if typical electrocardiogram changes were present along with prolonged chest pain, refractory to sublingual nitrates and/or enzyme or troponin T elevations (>0.1 g/L). Non ST-elevation myocardial infarction was diagnosed, if symptoms and troponin T criteria, but not the ECG criteria for ST-elevation myocardial infarction were met (13). The functional capacity of patients with cardiac disease, especially heart failure, was estimated according to a classification developed by the New York Heart Association (NYHA) (13). Left ventricular function was estimated using echocardiography (13).

AtheroGene

A total of 3,800 patients, who underwent coronary angiography at the Department of Medicine II of the Johannes Gutenberg-University Mainz or the Bundeswehr-Zentralkrankenhaus Koblenz, were recruited between June 1999 and March 2000 (15, 16). The exclusion criteria were evidence of hemodynamically significant valvular heart disease, surgery or trauma within the previous month, known cardiomyopathy, known cancer, febrile conditions, or use of oral anticoagulant therapy within the previous four weeks (15, 16). Subjects with missing information on the clinical presentation of CAD, missing laboratory measurements or missing information on the cause of death were additionally ruled out resulting in a subgroup 3,413 participants for the present analyses. CAD was diagnosed if the coronary angiogram showed at least one stenosis >30 % in a major coronary artery. Unstable angina was diagnosed according to Braunwald. Acute myocardial infarction was either ST-segment elevation with significant elevation in at least two contiguous leads or non-ST elevation myocardial infarction based on clinic and positive in-house troponin concentrations (16).

ESTHER

A total of 9,949 subjects were recruited for the “Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung (German)“ by their general practitioners during a routine health check-up between 2000 and 2002 in the German federal state Saarland (17, 18). The distribution of socio-demographic baseline characteristics and common prevalent chronic diseases were similar to the distribution in the respective age categories in the German National Health Survey, which is a representative sample of the German population (17), a fact supporting the population-based character of the study. We excluded study participants due to unmeasured HDL cholesterol, due to an unknown cause of death, and due to self-reported history of CAD

that was not physician-confirmed, leaving a subgroup of 5,738 participants for the present analysis. CAD was defined by physician-reported CAD (17, 18).

Ethical approval and written informed consent

All three studies were approved by the local ethics committees and performed in accordance with the declaration of Helsinki. All participants gave written informed consent (13-18).

Follow-up

In the LURIC cohort, there was a follow-up for cardiovascular mortality with a mean ± standard deviation duration of 8.9 ± 3.0 years (median and interquartile range: 9.9, 8.7-10.7). Information on the vital status was obtained from local person registries. Using death certificates two experienced clinicians independently classified the causes of death. They were masked to any other data of the study participants. In a few cases of a disagreement or uncertainty concerning the coding of a specific cause of death, classification was made by a principal investigator of the LURIC study (W. M.) (13). In the Athero*Gene* cohort, there was a follow-up for cardiovascular mortality with a mean ± standard deviation duration of 4.5 ± 2.0 years (median and interquartile range: 4.4, 2.9-6.3). Information about the causes of death and clinical events was obtained from hospital and general-practitioner charts. In the ESTHER cohort, there was a follow-up for cardiovascular mortality with a mean ± standard deviation duration of 9.1 ± 1.6 years (median and interquartile range: 9.4, 8.9-9.9). Deaths were identified by inquiry at the residents' registration offices. All deaths coded with ICD-10-codes I00-I99 were considered to be cardiovascular deaths.

Laboratory analyses

All analyses were performed in fasting blood samples. In the LURIC and Athero*Gene* cohorts, the blood samples were collected before angiography (13-16). In the ESTHER cohort, the blood samples were taken during the health check-up (17, 18).

In the LURIC cohort, the lipoproteins were separated using a combined ultracentrifugation-precipitation method (ß quantification) (13). Cholesterol was measured with enzymatic reagents from WAKO (Neuss, Germany) on a WAKO 30 R or Olympus AU640 (Tokyo, Japan) analyzer (13). Triglycerides were quantified with an enzymatic colour assay on a Hitachi 717 analyzer (Roche, Mannheim, Germany) (13). Apoplipoproteins A1, A2, and B were measured by turbidimetry (Rolf-Greiner Biochemica, Flacht, Germany) (13). In the Athero*Gene* cohort, total cholesterol, triglycerides were measured enzymatically (Roche Diagnostics, Mannheim, Germany). HDL cholesterol was measured after masking apolipoprotein B immunologically (Rolf Greiner Biochemica, Flacht, Germany). LDL cholesterol was calculated by the Friedewald formula (15, 16). In the ESTHER cohort, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were measured with standard methods (17, 18).

Statistical analysis

Tertiles of HDL cholesterol were formed in each cohort. The baseline characteristics are presented as counts and percentages of subjects in cases of categorical data and as means and standard deviations or medians with inter-quartile ranges in cases of continuous data for the tertiles of HDL cholesterol. The χ^2-test and ANalysis Of VAriance were used to compare the distributions of the variables across the tertiles of HDL cholesterol. Triglycerides (Shapiro-Wilk *W* test) were transformed logarithmically before being used in parametric statistical procedures. The Cox proportional hazards model was used to examine the association between HDL cholesterol and time to cardiovascular death. For exploratory purposes, the

associations of the HDL cholesterol tertiles with cardiovascular mortality were first studied in the entire LURIC cohort. Two predefined models of adjustment were used (model 1: adjusted for sex, age, and CAD; model 2: adjusted for sex, age, body mass index, systolic and diastolic blood pressure, diabetes mellitus, smoking, glomerular filtration rate, triglycerides, low density lipoprotein cholesterol, medication use (insulin, oral antidiabetic, ß-Blocker, ACE inhibitor, calcium antagonist, diuretic, acetyl salicylic acid, and statin), and CAD). Moreover, the interaction between the HDL cholesterol tertiles and CAD with regard to cardiovascular mortality was studied by including the interaction term as a covariate. In the next step, stratified analyses in people without CAD, in patients with stable CAD, and in patients with unstable CAD were conducted using the aforementioned models of adjustment. For replication, the associations of the HDL cholesterol tertiles with cardiovascular mortality were studied in the Athero*Gene* and ESTHER cohorts, which were stratified accordingly. All statistical tests were 2-sided and p values <0.05 were considered significant. The SPSS 19.0 statistical package (SPSS Inc., Chicago, USA) was used in the LURIC and ESTHER cohorts. The R statistical software package (http://www.r-project.org) was used in the Athero*Gene* cohort. For meta-analyses of the results obtained from the LURIC, Athero*Gene*, and ESTHER cohorts, HRs were pooled by the inverse of the variance method in a fixed effects model with the software Comprehensive Meta-Analysis®.

Role of the funding source

The funding source was not involved in study design, in the collection, analysis, and interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

Results

LURIC

Baseline characteristics

The study participants (2,191 males, 950 females) had a mean ± standard deviation age of 62.6 ± 10.6 years, body mass index of 27.5 ± 4.1 kg/m², and HDL cholesterol of 38.9 ± 10.8 mg/dl. High HDL cholesterol was associated with female gender, lower body mass index and waist circumference, and lower proportion of subjects with diabetes mellitus (*table 1*). HDL cholesterol was positively related to total, low density lipoprotein, and very low density lipoprotein cholesterol and inversely related to triglycerides (*table 1*). Furthermore, HDL cholesterol was positively related to apolipoprotein A1, apolipoprotein A2, and inversely to apolipoprotein B (*table 1*). Prevalent stable and unstable CAD, cerebral vascular disease, and peripheral vascular disease were more frequent in people with low HDL cholesterol (*table 1*). Moreover, low HDL cholesterol went in parallel with impaired left ventricular function (*table 1*). Use of insulin, oral antidiabetics, ß-blockers, ACE-inhibitors, diuretics, statins, and acetyl salicylic acid were more frequent in subjects with low HDL cholesterol (*table 1*). The baseline characteristics stratified for patients without CAD, patients with stable CAD, and those with unstable CAD are shown in *supplementary table 1*. There were no major differences in the mean HDL cholesterol concentrations among the corresponding HDL cholesterol tertiles of the subgroups without CAD, with stable CAD, and with unstable CAD (*supplementary table 1*).

Prospective analyses

A total of 925 deaths occurred during follow-up. Among these, 590 were due to cardiovascular diseases. In the entire cohort, the HDL cholesterol tertiles were inversely related to cardiovascular mortality (p=0.009) (*table 2*). However, further investigations disclosed significant interaction between the HDL cholesterol tertiles and CAD with regard to

cardiovascular mortality in model 1 (p=0.146 and p=0.004 for 2nd and 3rd tertile versus 1st tertile, respectively) and in model 2 (p=0.178 and p=0.007 for 2nd and 3rd tertile versus 1st tertile, respectively). Subsequent analyses were therefore stratified by presence of CAD. By doing so, the tertiles of HDL cholesterol were strongly associated with cardiovascular mortality in participants without CAD (p=0.005), but not in participants with stable (p=0.162) or unstable (p=0.675) CAD (*table 3*). When we independently formed the HDL cholesterol tertiles within the subgroups resulting in similar numbers of participants for the three tertiles, the associations of the HDL-C tertiles with cardiovascular mortality still remained significant in participants without CAD, but not in participants with stable and unstable CAD (*data not shown*).

Athero*Gene*

Baseline characteristics

The study participants (2,568 males, 845 females) had a mean ± standard deviation age of 61.8 ± 10.0 years, body mass index of 27.5 ± 3.9 kg/m², and HDL cholesterol of 49.2 ± 14.6 mg/dl. The baseline characteristics of the Athero*Gene* cohort stratified for patients without CAD, patients with stable CAD, and those with unstable CAD are shown in *supplementary table 2*.

Prospective analyses

A total of 381 deaths occurred during follow-up. Among these, 264 were due to cardiovascular diseases. Low HDL cholesterol was strongly associated with increased cardiovascular mortality in people without CAD (*table 4*). The association between HDL cholesterol and cardiovascular mortality was less pronounced in patients with stable CAD and turned non-significant after multivariate adjustment (*table 4*). In patients with unstable CAD,

there was no significant association between the tertiles of HDL cholesterol and cardiovascular mortality (*table 4*).

ESTHER

Baseline characteristics

The study participants (2,606 males, 3,132 females) had a mean ± standard deviation age of 62.0 ± 6.6 years, body mass index of 27.7 ± 4.3 kg/m², and HDL cholesterol of 53.5 ± 15.3 mg/dl. The baseline characteristics of the ESTHER cohort stratified for people without CAD and patients with stable CAD are shown in *supplementary table 3*.

Prospective analyses

A total of 586 deaths occurred during the follow-up. Among these, 196 deaths were due to cardiovascular diseases. HDL cholesterol was inversely related to cardiovascular mortality in people without CAD (*table 4*). This association reached statistical significance comparing the 2nd to the 1st tertile of HDL cholesterol (*table 4*). In patients with stable CAD, there was no significant association between the tertiles of HDL cholesterol and cardiovascular mortality (*table 4*).

Meta-analysis

The meta-analysis comprised 12,292 participants of the LURIC, Athero*Gene* and ESTHER cohorts. In the subgroup of 5,791 people without CAD, the HDL cholesterol tertiles were significantly, inversely related to cardiovascular mortality (*table 5*). In contrast, the HDL cholesterol tertiles were not significantly related to cardiovascular mortality in the 4,304 patients with stable CAD and the 2,197 patients with unstable CAD (*table 5*).

Discussion

The present data from a total of 12,292 participants of the LURIC, the Athero*Gene*, and the ESTHER cohorts show that CAD modulates the association of HDL cholesterol with cardiovascular mortality.

HDL cholesterol tertiles were significantly, inversely related to cardiovascular mortality in the entire LURIC cohort. Inclusion of the interaction term between CAD and HDL cholesterol indicated variation in the predictive value of HDL cholesterol for cardiovascular mortality according to the presence of CAD. In stratified analyses, the association between the HDL cholesterol tertiles and cardiovascular mortality was strong in people without CAD whereas it was weak and non-significant after multivariate adjustment in patients with stable and unstable CAD. Very similar observations were made in the *AtheroGene* cohort. The aforementioned differences were less pronounced in the ESTHER cohort, possibly due to the lack of coronary angiograms and consequently a large proportion of undiagnosed, silent CAD. Finally, a meta-analysis comprising all three cohorts was performed and the results were in support of the LURIC findings.

Previous studies have not specifically addressed an interaction of HDL with CAD, probably because very few studies have collected precise information on both, CAD at baseline and cardiovascular death. However, our results are in agreement with evidence from the dal-OUTCOMES trial (12). In this cohort of 15,871 patients, who had suffered acute coronary syndromes, HDL cholesterol was not predictive of the primary end-point (12). Moreover, the present observations are confirmed by recent data on the cholesterol efflux capacity from macrophages to serum, which is positively related to HDL cholesterol (19, 20). In cross-sectional analyses, low cholesterol efflux capacity was repeatedly associated with higher prevalence of CAD (19, 20). At the same time, the cholesterol efflux capacity was positively associated with the risk of future vascular complications in patients with CAD whereas no such paradox association was seen in an outpatient cohort (20).

Two potential reasons, that may explain the interaction between the HDL cholesterol tertiles and CAD with regard to cardiovascular mortality, shall be highlighted: First, dysfunctional HDL may account for weaker associations of HDL cholesterol with cardiovascular mortality in CAD. HDL is considered to represent the major vehicle of reverse cholesterol transport (21-23). In addition, HDL may exert anti-inflammatory effects, prevent low-density lipoprotein oxidation, and play an important role in nitric oxide synthesis (21-23). Even anti-thrombotic potency has been suggested (21-23). Nevertheless, there is growing knowledge that the vascular protective properties of HDL are impaired in certain diseases (24, 25). Most importantly, the anti-inflammatory and anti-oxidative effects of HDL were demonstrated to be reduced in CAD (26, 27). In the LURIC cohort, the apolipoprotein A1 and A2 composition of HDL did not explain the key finding (*supplementary text*). Future studies within the LURIC cohort will address other aspects of HDL functionality. Second, multimodal treatment of cardiovascular risk factors and co-morbidity may have blunted the relationships of HDL cholesterol with cardiovascular mortality in patients with CAD. However, exploratory analyses within the LURIC cohort did not support this possibility (*supplementary text*).

It is a limitation of our study that HDL cholesterol was measured once at baseline only. Therefore, we were not able to adjust for possible moderate fluctuations of HDL cholesterol during the follow-up, for example due to the start of statin treatment or an increase of the statin dose (28). The major strength of this work is the detailed clinical and metabolic investigation of the LURIC participants including coronary angiography. Moreover, we want to emphasise the long duration of the follow-up with a large number of fatal cardiovascular events. In addition, our conclusions rely on replication in 3,413 participants of the Athero*Gene* cohort and 5,738 participants of the ESTHER cohort, and on a meta-analysis comprising all three cohorts.

To sum up, the association of HDL cholesterol with cardiovascular mortality is weakened in the presence of CAD. The usefulness of measuring HDL cholesterol for cardiovascular risk stratification may be limited in secondary prevention.

Contributions

B.O.B. and W.M. designed the LURIC study. G.S., W.M., and M.E.K. performed the statistical analysis in the LURIC cohort. H.S. performed lipid analysis in the LURIC cohort. G.S. wrote the manuscript. S.B. designed the Athero*Gene* study. S.A. performed the statistical analysis in the Athero*Gene* study. H.B. designed the ESTHER study. B.H. was responsible for mortality data collection in the ESTHER study. B.S. and U.M. performed the statistical analysis in the ESTHER study. B.S. performed the meta-analysis. T.B.G., A.R., H.S., U.L., H.B., B.S., R.S., S.B., G.G., and A.N. contributed to the interpretation of the results and reviewed/edited the manuscript. All authors have read, approved, and take full responsibility for the manuscript as submitted.

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Table 1

Title: Baseline characteristics according to tertile of HDL cholesterol in the LURIC cohort

	1st tertile	2nd tertile	3rd tertile	
Number	1048	1083	1010	**P**
Male sex	868 (82.8)	776 (71.7)	547 (54.2)	<0.001
Age, years	61.8±11.1	62.6±10.2	63.6±10.4	0.001
Body mass index, kg/m²	28.1±4.1	27.8±4.1	26.6±3.9	<0.001
Waist circumference, cm †	101±11	100±11	96±12	<0.001
Hypertension	767 (73.2)	798 (73.7)	732 (72.5)	0.822
Systolic blood pressure, mmHg	139±24	142±23	143±23	0.001
Diastolic blood pressure, mmHg	80±12	82±11	82±11	<0.001
Diabetes mellitus	510 (48.7)	438 (40.4)	293 (29.0)	<0.001
Smoking				<0.001
Never	285 (27.2)	383 (35.4)	468 (46.3)	
Former smoker	504 (48.1)	492 (45.4)	410 (40.6)	
Current smoker	259 (24.7)	208 (19.2)	132 (13.1)	
Lipids‡				
Total cholesterol, mg/dl	182±41	194±37	203±36	<0.001
LDL cholesterol, mg/dl	106±35	120±33	124±33	<0.001
HDL cholesterol, mg/dl	28±4	38±3	51±8	<0.001
VLDL cholesterol, mg/dl	46±33	37±24	28±18	<0.001
Triglycerides, mg/dl	173 (128-241)	149 (114-201)	122 (93-161)	<0.001§
Apolipoprotein A1, mg/dl	108±15	128±13	155±19	<0.001
Apolipoprotein A2, mg/dl	36±8	42±8	48±9	<0.001
Apolipotrotein B, mg/dl	106±26	106±24	101±23	<0.001
GFR, ml/min/1.73m²	80±20	83±19	81±18	0.022
Coronary artery disease				<0.001
No CAD	142 (13.5)	233 (21.5)	324 (32.1)	
Stable CAD	509 (48.6)	535 (49.4)	471 (46.6)	
Unstable CAD	397 (37.9)	315 (29.1)	215 (21.3)	
Presentation of unstable CAD				<0.001
Unstable Angina	223 (21.3)	217 (20.0)	181 (17.9)	
NSTEMI	61 (5.8)	34 (3.1)	19 (1.9)	
STEMI	113 (10.8)	64 (5.9)	15 (1.5)	
NYHA functional class				0.339
1	527 (50.3)	569 (52.5)	509 (50.4)	
2	302 (28.8)	319 (29.5)	314 (31.1)	
3	189 (18.0)	157 (14.5)	157 (15.5)	
4	30 (2.9)	38 (3.5)	30 (3.0)	
Left ventricular function (echo) ‖				<0.001
Normal	542 (53.1)	665 (62.9)	723 (72.7)	
Mildly impaired	163 (16.0)	155 (14.7)	116 (11.7)	
Moderately impaired	136 (13.3)	123 (11.6)	76 (7.6)	
Severely impaired	77 (7.5)	36 (3.4)	28 (2.8)	
Peripheral vascular disease	147 (14.0)	86 (7.9)	66 (6.5)	<0.001
Cerebrovascular disease	123 (11.7)	87 (8.0)	76 (7.5)	0.001
Medication use				
Insulin	70 (6.7)	59 (5.4)	38 (3.8)	0.013
Oral antidiabetic	125 (11.9)	84 (7.8)	46 (4.6)	<0.001
ß-Blocker	730 (69.7)	697 (64.4)	552 (54.7)	<0.001
ACE inhibitor	637 (60.8)	565 (52.2)	455 (45.0)	<0.001
Calcium antagonist	156 (14.9)	169 (15.6)	174 (17.2)	0.331
Diuretic	366 (34.9)	286 (26.4)	244 (24.2)	<0.001
Statin	576 (54.9)	530 (48.9)	408 (40.4)	<0.001

Acetyl salicylic acid	790 (75.4)	773 (71.4)	672 (66.5)	<0.001

Legend: Values are means ± standard deviations or medians (25^{th}-75^{th} percentiles) in cases of continuous variables and numbers (percentages) in case of categorical data; * for differences across the three groups calculated with chi-square test and ANalysis Of VAriance for categorical and continuous data, respectively; † numbers: 1035/1073/994; ‡ to convert values for total, LDL, HDL, and VLDL cholesterol to millimoles per liter, multiply by 0.02586; to convert values for triglycerides to millimoles per liter, multiply by 0.01129; § ANalysis Of VAriance of logarithmically transformed values; || numbers: 918/979/943

Table 2

Title: Cardiovascular mortality according to tertile of HDL cholesterol in the LURIC cohort

	N	CD	HR	P
Model 1 *				
1st tertile	1048	248 (23.7)	1.0 reference	
2nd tertile	1083	190 (17.5)	0.71 (0.59-0.86)	<0.001
3rd tertile	1010	152 (15.0)	0.59(0.36-0.80)	<0.001
Model 2 †				
1st tertile	1048	248 (23.7)	1.0 reference	
2nd tertile	1083	190 (17.5)	0.82 (0.67-1.00)	0.052
3rd tertile	1010	152 (15.0)	0.74 (0.59-0.93)	0.009

Legend: N number; CD number of cardiovascular deaths (percentage of tertile); HR hazard ratio (calculated with Cox proportional hazards model); * adjusted for sex, age, and CAD; † adjusted for sex, age, body mass index, systolic and diastolic blood pressure, diabetes, smoking, glomerular filtration rate, triglycerides, LDL cholesterol, medication use (insulin, oral antidiabetic, ß-Blocker, ACE inhibitor, calcium antagonist, diuretic, acetyl salicylic acid, and statin), and CAD

Table 3

Title: Cardiovascular mortality according to tertile of HDL cholesterol stratified for CAD in the LURIC cohort

	No CAD				Stable CAD				Unstable CAD			
	N	**CD**	**HR**	**P**	**N**	**CD**	**HR**	**P**	**N**	**CD**	**HR**	**P**
Model 1 *												
1st tertile	142	22 (15.5)	1.0 reference		509	138 (27.1)	1.0 reference		397	88 (22.2)	1.0 reference	
2nd tertile	233	20 (8.6)	0.44 (0.24-0.81)	0.008	535	114 (21.3)	0.74 (0.58-0.95)	0.017	315	56 (17.8)	0.75 (0.53-1.04)	0.085
3rd tertile	324	19 (5.9)	0.27 (0.14-0.50)	<0.001	471	94 (20.0)	0.67 (0.51-0.87)	0.003	215	39 (18.1)	0.65 (0.44-0.96)	0.030
Model 2 †												
1st tertile	142	22 (15.5)	1.0 reference		505	138 (27.1)	1.0 reference		397	88 (22.2)	1.0 reference	
2nd tertile	233	20 (8.6)	0.54 (0.28-1.06)	0.074	535	114 (21.3)	0.83 (0.64-1.08)	0.162	315	56 (17.8)	0.88 (0.62-1.26)	0.485
3rd tertile	324	19 (5.9)	0.37 (0.18-0.74)	0.005	471	94 (20.0)	0.81 (0.61-1.09)	0.159	215	39 (18.1)	0.91 (0.59-1.41)	0.675

Legend: N number; CD number of cardiovascular deaths (percentage of tertile); HR hazard ratio (calculated with Cox proportional hazards model); * adjusted for sex and age; † adjusted for sex, age, body mass index, systolic and diastolic blood pressure, diabetes, smoking, glomerular filtration rate, triglycerides, LDL cholesterol, and medication use (insulin, oral antidiabetic, ß-Blocker, ACE inhibitor, calcium antagonist, diuretic, acetyl salicylic acid, and statin)

Table 4

Title: Cardiovascular mortality according to tertile of HDL cholesterol stratified for CAD in the ESTHER and Athero*Gene* cohorts

	No CAD				Stable CAD				Unstable CAD			
	N	**CD**	**HR**	**P**	**N**	**CD**	**HR**	**P**	**N**	**CD**	**HR**	**P**
Athero*Gene*												
Model 1 *												
1st tertile	35	6 (17.1)	1.0 reference		674	65 (9.6)	1.0 reference		509	46 (9.0)	1.0 reference	
2nd tertile	45	2 (4.4)	0.29 (0.06-1.44)	0.128	643	39 (6.1)	0.65 (0.43-0.96)	0.031	421	36 (8.6)	0.95 (0.62-1.48)	0.828
3rd tertile	73	2 (2.7)	0.16 (0.03-0.82)	0.027	673	42 (6.2)	0.57 (0.38-0.86)	0.007	340	26 (7.6)	0.68 (0.42-1.12)	0.127
Model 2 †												
1st tertile	n.a. ‡	n.a. ‡	n.a. ‡	n.a. ‡	663	65 (9.8)	1.0 reference		503	45 (8.9)	1.0 reference	
2nd tertile					633	38 (6.0)	0.88 (0.58-1.33)	0.539	416	36 (8.7)	1.06 (0.67-1.69)	0.792
3rd tertile					659	41 (6.2)	0.73 (0.47-1.13)	0.159	337	26 (7.7)	0.90 (0.53-1.52)	0.685
ESTHER												
Model 1 *												
1st tertile	1546	47 (3.0)	1.0 reference		362	37 (10.2)	1.0 reference		n.a. §	n.a. §	n.a. §	n.a. §
2nd tertile	1665	29 (1.7)	0.58 (0.36-0.92)	0.020	255	29 (11.4)	1.18 (0.72-1.93)	0.502				
3rd tertile	1728	35 (2.0)	0.74 (0.46-1.17)	0.199	182	19 (10.4)	1.14 (0.64-2.02)	0.659				
Model 2 †												
1st tertile	1184	37 (3.1)	1.0 reference		282	26 (9.2)	1.0 reference					
2nd tertile	1324	23 (1.7)	0.58 (0.34-1.00)	0.050	211	24 (11.4)	1.80 (0.98-3.33)	0.059				
3rd tertile	1410	29 (2.1)	0.80 (0.50-1.27)	0.226	151	14 (9.3)	1.70 (0.80-3.61)	0.168				

Legend: N number; CD number of cardiovascular deaths (percentage of tertile); HR hazard ratio; * adjusted for sex and age; † adjusted for sex, age, body mass index, systolic and diastolic blood pressure (hypertension in the Athero*Gene* cohort), diabetes, smoking, glomerular filtration rate,

triglycerides, LDL cholesterol, and medication use (insulin, oral antidiabetic, ß-Blocker, ACE inhibitor, calcium antagonist, diuretic, acetyl salicylic acid, and statin); ‡ sample size too low; § no patients with unstable CAD in this cohort

Table 5

Title: Results of meta-analyses for cardiovascular mortality according to tertile of HDL cholesterol stratified for coronary artery disease in the LURIC, ESTHER and Athero*Gene* cohorts

	No CAD			Stable CAD			Unstable CAD		
	HR	**P**	**Heterogeneity (Q; P; I^2)**	**HR**	**P**	**Heterogeneity (Q; P; I^2)**	**HR**	**P**	**Heterogeneity (Q; P; I^2)**
Model 1 *									
1st tertile	1.0 reference			1.0 reference			1.0 reference		
2nd tertile	0.51 (0.35-0.73)	<0.001	1.0; 0.61; 0%	0.77 (0.64-0.94)	0.009	3.7; 0.16; 45%	0.82 (0.63-1.07)	0.143	0.7; 0.40; 0%
3rd tertile	0.49 (0.34-0.71)	<0.001	8.1; 0.02; 75%	0.67 (0.56-0.85)	<0.001	3.8; 0.14; 48%	0.66 (0.49-0.90)	0.008	0.2; 0.88; 0%
Model 2†‡									
1st tertile	1.0 reference			1.0 reference			1.0 reference		
2nd tertile	0.56 (0.37-0.86)	0.007	0.0; 0.87; 0%	0.92 (0.75-1.13)	0.440	5.3; 0.07; 62%	0.94 (0.71-1.25)	0.681	0.4; 0.53; 0%
3rd tertile	0.63 (0.43-0.94)	0.021	3.2; 0.07; 68%	0.84 (0.67-1.06)	0.148	3.8; 0.15; 48%	0.91 (0.65-1.27)	0.564	0.0; 0.98; 0%

Legend: HR hazard ratio; * adjusted for sex and age; † adjusted for sex, age, body mass index, systolic and diastolic blood pressure, diabetes, smoking, glomerular filtration rate, triglycerides, LDL cholesterol, and medication use (insulin, oral antidiabetic, ß-Blocker, ACE inhibitor, calcium antagonist, diuretic, acetyl salicylic acid, and statin); for participants without CAD including data from LURIC and Athero*Gene* cohorts only

Supplementary text

LURIC

Clinical characterisation

Information on socio-demographic characteristics, lifestyle and a history of common diseases were obtained by a comprehensive questionnaire from the study participants and from medical records at baseline (1).

Diabetes mellitus was newly diagnosed according to the 2010 criteria of the American Diabetes Association. Thus, participants were categorised as diabetic if fasting plasma glucose was ≥126 mg/dl and/or plasma post-challenge glucose (plasma glucose 2 hours after the 75g glucose load) was ≥200 mg/dl and/or glycated hemoglobin was ≥6.5% (2). Moreover patients with a history of diabetes and those using oral anti-diabetics or insulin were considered diabetic.

Hypertension was diagnosed if the systolic and/or diastolic blood pressure exceeded 140 and/or 90 mmHg or if there was a history of hypertension, evident through the use of antihypertensive drugs (1).

Cerebrovascular disease was defined clinically by documented history of a previous cerebrovascular disease event (transient ischaemic attack, prolonged ischaemic neurological deficit, cerebral infarction with or without a remaining neurological deficit) or by documented carotid plaques (≥50 % luminal obstruction) (1).

Peripheral vascular disease was defined by a history of intermittent claudication, angiographic documentation of atherosclerotic luminal obstruction of the peripheral arteries or a history of a peripheral arterial intervention for atherosclerotic disease (angioplasty or surgery) (1).

Laboratory examination

Creatinine was measured with the Jaffé method on a Hitachi 717 analyzer (1). The estimated glomerular filtration rate was calculated as previously described (3).

Statistical analysis

Analyses on HDL functionality: ANalysis Of VAriance models adjusted for the HDL cholesterol tertiles, sex, age, CAD, and the interaction term between the HDL cholesterol tertiles and CAD were performed to test whether the distributions of the apolipoproteins A1 and A2 across the tertiles of HDL cholesterol differ among the different CAD categories.

Analyses on cardiovascular mortality with adjustment for potential confounders: Interaction terms between the HDL cholesterol tertiles and medication use and clinical and biochemical characteristics were included in Cox model 2 to test whether the interaction between the HDL cholesterol tertiles and CAD independently predicts cardiovascular mortality.

Results

Analyses on HDL functionality: The interaction term between the HDL cholesterol tertiles and CAD was not associated with the apolipoproteins A1 (p=0.900) and A2 (p=0.987).

Analyses on cardiovascular mortality with adjustment for potential confounders: The association of the interaction term between the HDL cholesterol tertiles and CAD with cardiovascular mortality remained significant (p=0.196 and p=0.023 for 2^{nd} and 3^{rd} tertile versus 1^{st} tertile, respectively) after inclusion of the interaction term between the HDL cholesterol tertiles and statin use in model 2. Significance for the interaction term between the HDL cholesterol tertiles and CAD with regard to cardiovascular mortality was also observed after inclusion of the interaction terms between the HDL cholesterol tertiles and use of acetyl salicylic acid (p=0.256 and p=0.017 for 2^{nd} and 3^{rd} tertile versus 1^{st} tertile, respectively), ß-blockers (p=0.246 and p=0.007 for 2^{nd} and 3^{rd} tertile versus 1^{st} tertile, respectively), ACE

inhibitors (p=0.150 and p=0.005 for 2nd and 3rd tertile versus 1st tertile, respectively), calcium antagonists (p=0.169 and p=0.006 for 2nd and 3rd tertile versus 1st tertile, respectively), diuretics (p=0.201 and p=0.008 for 2nd and 3rd tertile versus 1st tertile, respectively), oral antidiabetics (p=0.171 and p=0.007 for 2nd and 3rd tertile versus 1st tertile, respectively), and insulin (p=0.162 and p=0.005 for 2nd and 3rd tertile versus 1st tertile, respectively). The interaction between the HDL cholesterol tertiles and CAD also remained a significant predictor of cardiovascular mortality after adjustment for the interaction between the HDL cholesterol tertiles and gender (p=0.212 and p=0.010 for 2nd and 3rd tertile versus 1st tertile, respectively), age (p=0.221 and p=0.017 for 2nd and 3rd tertile versus 1st tertile, respectively), body mass index (p=0.218 and p=0.007 for 2nd and 3rd tertile versus 1st tertile, respectively), diabetes mellitus (p=0.169 and p=0.005 for 2nd and 3rd tertile versus 1st tertile, respectively), systolic blood pressure (p=0.196 and p=0.012 for 2nd and 3rd tertile versus 1st tertile, respectively), diastolic blood pressure (p=0.165 and p=0.010 for 2nd and 3rd tertile versus 1st tertile, respectively), glomerular filtration rate (p=0.174 and p=0.010 for 2nd and 3rd tertile versus 1st tertile, respectively), LDL cholesterol (p=0.194 and p=0.010 for 2nd and 3rd tertile versus 1st tertile, respectively), triglycerides (p=0.194 and p=0.010 for 2nd and 3rd tertile versus 1st tertile, respectively), and smoking (p=0.172 and p=0.006 for 2nd and 3rd tertile versus 1st tertile, respectively).

Athero*Gene*

Clinical characterisation

Information on socio-demographic characteristics, lifestyle and a history of common diseases were obtained by a comprehensive questionnaire from the study participants and from medical records at baseline (4).

Diabetes mellitus was diagnosed if fasting plasma glucose was ≥126 mg/dl. Moreover, patients with a history of diabetes and those using oral anti-diabetics or insulin were considered diabetic (4).

Hypertension was diagnosed if there was a history of hypertension or ongoing use of antihypertensive drugs (4)

Laboratory examination

Creatinine was measured with was measured by the modified Jaffe routine method (5). Estimated glomerular filtration rate was calculated according to the Cockroft–Gault (6)

ESTHER

Clinical characterisation

Information on socio-demographic characteristics, lifestyle and a history of common diseases were obtained by a comprehensive questionnaire from the study participants at baseline.

Diabetes mellitus was diagnosed based on reports of physicians. In addition, diabetes was identified by use of anti-diabetic medication and/or fasting plasma glucose ≥126 mg/dl and/or non-fasting glucose ≥200 mg/dl and/or glycated hemoglobin ≥6.5% (7).

Hypertension was diagnosed based on reports of physicians. In addition, hypertension was identified by use of antihypertensive drugs and/or self-reported hypertension plus a systolic blood pressure ≥140 and/or a diastolic blood pressure ≥90 mmHg.

Cerebrovascular disease was self-reported by study participants in the standardized questionnaire in a question on any kind of stroke in the past.

Peripheral vascular disease was defined by a self-reported history of a balloon dilatation of the of leg arteries.

Laboratory examination

Serum creatinine was determined by kinetic Jaffé method (8). Estimated glomerular filtration rate was calculated according to the Modification of Diet in Renal Disease equation (9)

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Supplementary table 1

Title: Baseline characteristics according to tertile of HDL cholesterol in LURIC stratified for CAD

	No CAD				Stable CAD				Unstable CAD			
	1st tertile	**2nd tertile**	**3rd tertile**	**P***	**1st tertile**	**2nd tertile**	**3rd tertile**	**P***	**1st tertile**	**2nd tertile**	**3rd tertile**	**P***
Number	142	233	324		509	535	471		397	315	215	
Male sex	37 (26.1)	109 (46.8)	190 (58.6)	<0.001	432 (84.9)	419 (78.3)	294 (62.4)	<0.001	331 (83.4)	233 (74.0)	119 (55.3)	<0.001
Age, years	55.6±13.0	58.0±11.3	59.7±11.5	0.002	63.1±10.3	63.8±9.1	65.2±9.1	0.002	62.5 ±10.8	63.7 ± 10.1	65.7 ± 9.6	0.001
Body mass index, kg/m²	28.2±4.3	28.0±4.6	26.7±4.0	<0.001	28.1±4.1	27.8±4.0	26.5±3.7	<0.001	28.0 ± 4.2	27.8 ± 3.7	26.6 ± 4.0	<0.001
Waist circumference, cm †	100±12	98±12	94±12	<0.001	101±11	100±12	97±12	<0.001	102 ± 12	101 ± 10	97 ± 12	<0.001
Hypertension	89 (62.7)	148 (63.5)	206 (63.6)	0.981	392 (77.0)	415 (77.6)	363 (77.1)	0.973	286 (72.0)	235 (74.6)	163 (75.8)	0.551
Systolic blood pressure, mmHg	132±22	138±22	137±23	0.029	143±23	146±23	147±23	0.005	137±25	140±22	141±21	0.140
Diastolic blood pressure, mmHg	78±12	81±11	81±11	0.030	81±11	83±11	83±11	0.006	79±12	80±11	81±11	0.139
Diabetes mellitus	56 (39.4)	69 (29.6)	62 (19.1)	<0.001	260 (51.1)	223 (41.7)	165 (35.0)	<0.001	194 (48.9)	146 (46.3)	66 (30.7)	<0.001
Smoking				0.001				<0.001				<0.001
Never	55 (38.7)	119 (51.1)	186 (57.4)		129 (25.3)	164 (30.7)	196 (41.6)		101 (25.4)	100 (31.7)	86 (40.0)	
Former smoker	53 (37.3)	63 (27.0)	96 (29.6)		278 (54.6)	286 (53.5)	220 (46.7)		173 (43.6)	143 (45.4)	94 (43.7)	
Current smoker	34 (23.9)	51 (21.9)	42 (12.0)		102 (20.0)	85 (15.9)	55 (11.7)		123 (31.0)	72 (22.9)	35 (16.3)	
Lipids‡												
Total cholesterol, mg/dl	183±43	197±35	207±32	<0.001	182±40	197±37	203±38	<0.001	180 ± 40	187 ± 37	198 ± 35	<0.001
LDL cholesterol, mg/dl	103±31	122±31	126±29	<0.001	106±36	121±32	124±35	<0.001	108 ± 35	116 ± 32	122 ± 32	<0.001
HDL cholesterol, mg/dl	29±4	38±3	53±9	<0.001	28±4	38±3	51±7	<0.001	28 ± 4	37 ± 2	51 ± 8	<0.001
VLDL cholesterol, mg/dl	50±44	37±22	28±19	<0.001	47±32	38±26	29±18	<0.001	44 ± 29	34 ± 20	51 ± 8	<0.001
Triglycerides, mg/dl	172 (120-267)	147 (109-208)	115 (88-156)	<0.001	173 (127-242)	148 (112-201)	122 (94-164)	<0.001	172 (133-230)	153 (118-196)	129 (98-162)	<0.001
Apolipoprotein A1, mg/dl	109±17	130±13	158±21	<0.001	109±15	129±13	155±18	<0.001	105±14	125±13	152±18	<0.001
Apolipoprotein A2, mg/dl	36±8	42±7	49±10	<0.001	36±8	42±8	48±9	<0.001	35±8	41±7	46±8	<0.001
Apolipotrotein B, mg/dl	103±24	106±23	100±21	0.007	106±26	107±24	103±25	0.017	108±28	104±24	100±23	0.001
GFR, ml/min/1.73m²	83±20	84±17	82±17	0.587	80±20	83±18	82±18	0.063	79±21	81±20	79±18	0.540
Presentation of unstable CAD												<0.001
Unstable angina	0	0	0	n.a.	0	0	0	n.a.	223 (56.2)	217 (68.9)	181 (84.2)	
NSTEMI	0	0	0		0	0	0		61 (15.4)	34 (10.8)	19 (8.8)	

STEMI	0	0	0		0	0	0		113 (28.5)	64 (20.3)	15 (7.0)	
NYHA functional class				0.424				0.152				0.044
1	65 (45.8)	108 (46.4)	163 (50.3)		236 (46.4)	287 (53.6)	235 (49.9)		226 (56.9)	174 (55.2)	111 (51.6)	
2	47 (33.1)	82 (35.2)	109 (33.6)		159 (31.2)	160 (29.9)	153 (32.5)		96 (24.2)	77 (24.4)	52 (24.2)	
3	28 (19.7)	38 (16.3)	41 (12.7)		98 (19.3)	79 (14.6)	73 (15.5)		63 (15.9)	40 (12.7)	43 (20.0)	
4	2 (1.4)	5 (2.1)	11 (3.4)		16 (3.1)	9 (1.7)	10 (2.1)		12 (9.0)	24 (7.6)	9 (4.2)	
Left ventricular function (echo) ‖				<0.001				<0.001				<0.001
Normal	87 (62.1)	160 (70.8)	255 (80.2)		269 (55.5)	326 (62.7)	322 (69.7)		186 (47.1)	179 (57.6)	146 (68.2)	
Mildly impaired	12 (8.6)	24 (10.6)	32 (10.1)		89 (18.4)	82 (15.8)	62 (13.4)		62 (15.7)	49 (15.8)	22 (10.3)	
Moderately impaired	18 (12.9)	26 (11.5)	16 (5.0)		75 (15.5)	68 (13.1)	48 (10.4)		43 (10.9)	29 (9.3)	12 (5.6)	
Severely impaired	18 (12.9)	9 (4.0)	7 (2.2)		37 (7.6)	18 (3.5)	14 (3.0)		22 (5.6)	9 (2.9)	7 (3.3)	
Peripheral vascular disease	4 (2.8)	5 (2.1)	6 (1.9)	0.803	83 (16.3)	59 (11.0)	42 (8.9)	0.001	60 (15.1)	22 (7.0)	18 (8.4)	0.001
Cerebrovascular disease	9 (6.3)	17 (7.3)	15 (4.6)	0.403	75 (14.7)	41 (7.7)	34 (7.2)	<0.001	39 (9.8)	29 (9.2)	27 (12.6)	0.428
Medication use												
Insulin	2 (1.4)	4 (1.7)	1 (0.3)	0.222	38 (7.5)	38 (7.1)	25 (5.3)	0.353	30 (7.6)	17 (5.4)	12 (5.6)	0.435
Oral antidiabetic	10 (7.0)	9 (3.9)	6 (1.9)	0.020	59 (11.6)	48 (9.0)	30 (6.4)	0.017	56 (14.1)	27 (8.6)	10 (4.7)	0.001
ß-Blocker	64 (45.1)	116 (49.8)	131 (40.4)	0.090	348 (68.4)	334 (62.4)	266 (56.5)	<0.001	318 (80.1)	247 (78.4)	155 (72.1)	0.070
ACE inhibitor	60 (42.3)	90 (38.6)	101 (31.2)	0.041	298 (58.5)	276 (51.6)	234 (49.7)	0.013	279 (70.3)	199 (63.2)	120 (55.8)	0.001
Calcium antagonist	15 (10.6)	34 (14.6)	45 (13.9)	0.514	91 (17.9)	94 (17.6)	92 (19.5)	0.694	50 (12.6)	41 (13.0)	37 (17.2)	0.253
Diuretic	54 (38.0)	57 (24.5)	66 (20.4)	<0.001	197 (38.7)	151 (28.2)	120 (25.5)	<0.001	115 (29.0)	78 (24.8)	58 (27.0)	0.455
Statin	34 (23.9)	41 (17.6)	52 (16.0)	0.122	267 (52.5)	284 (53.1)	232 (49.3)	0.438	274 (69.0)	205 (65.1)	124 (57.7)	0.019
Acetyl salicylic acid	52 (36.6)	109 (46.8)	136 (42.0)	0.150	385 (75.6)	387 (72.3)	350 (74.3)	0.472	353 (88.9)	277 (87.9)	186 (86.5)	0.681

Legend: Values are numbers (percentages) for categorical data and means ± standard deviations or medians (25^{th}-75^{th} percentiles) for continuous variables; * for differences across the three groups calculated with chi-square test and ANalysis Of VAriance for categorical and continuous data, respectively; † number: 140/232/321/501/528/463/394/313/210; ‡ to convert values for total, LDL, HDL, and VLDL cholesterol to millimoles per liter, multiply by 0.02586; to convert values for triglycerides to millimoles per liter, multiply by 0.01129; § ANalysis Of VAriance of logarithmically transformed values; ‖ number 140/226/318/485/520/462/395/311/214

Supplementary table 2

Title: Baseline characteristics according to tertile of HDL cholesterol in Athero*Gene* stratified for CAD

	No CAD				Stable CAD				Unstable CAD			
	1st tertile	**2nd tertile**	**3rd tertile**	**P***	**1st tertile**	**2nd tertile**	**3rd tertile**	**P***	**1st tertile**	**2nd tertile**	**3rd tertile**	**P***
Number	35	45	73		674	643	673		509	421	340	
Male sex	16 (45.7)	28 (62.2)	31 (42.5)	0.100	587 (87.1)	537 (83.5)	417 (62)	<0.001	421 (82.7)	327 (77.7)	204 (60)	<0.001
Age, years	59.0±10.5	57.9±9.3	62.8±9.4	0.017	61.3±10	61.7±9.7	63.7±9	<0.001	60.2±10.9	60.6±10.5	64.1±9.8	<0.001
Body mass index, kg/m²	28.3±4.4	27.5±3.7	26.1±3.7	0.015	28.4±3.9	27.6±4.1	26.6±3.8	<0.001	28.1±4	27.2±3.7	26.5±3.7	<0.001
Waist circumference, cm	n.a.	n.a.	n.a.		n.a.	n.a.	n.a.		n.a.	n.a.	n.a.	
Hypertension	20 (57.1)	25 (55.6)	46 (63.0)	0.69	535 (79.4)	502 (78.1)	537 (79.8)	0.73	370 (72.7)	271 (64.4)	230 (67.6)	0.022
Diabetes mellitus	9 (25.7)	4 (8.9)	6 (8.2)	0.025	205 (30.4)	130 (20.2)	123 (18.3)	<0.001	125 (24.6)	71 (16.9)	62 (18.2)	0.008
Smoking				0.583				<0.001				<0.001
Never	20 (57.1)	22 (48.9)	47 (64.4)		222 (32.9)	230 (35.8)	286 (42.5)		154 (30.3)	150 (35.6)	157 (46.2)	
Former smoker	4 (11.4)	6 (13.3)	6 (8.2)		240 (35.6)	244 (37.9)	240 (35.7)		183 (36)	154 (36.6)	96 (28.2)	
Current smoker	11 (31.4)	17 (37.8)	20 (27.4)		212 (31.5)	169 (26.3)	147 (21.8)		171 (33.7)	117 (27.8)	87 (25.6)	
Lipids †												
Total cholesterol, mg/dl	220±34	224±38	230±45	0.50	189±46	203±47	219±46	<0.001	195±46	214±43	224±47	<0.001
LDL cholesterol, mg/dl	140±30	146±33	136±39	0.29	119±40	129±42	132±44	<0.001	125±40	139±42	137±41	<0.001
HDL cholesterol, mg/dl	35±5	48±3.4	70±14	<0.001	36±5	48±3	66±12	<0.001	36±6	48±3	65±12	<0.001
Triglycerides, mg/dl	205 (160-273)	140 (98-196)	109 (77- 156)	<0.001	165 (119-232)	134 (98- 185)	109 (82-145)	<0.001	159 (115-224)	137 (102-189)	105 (80-141)	<0.001
GFR, ml/min/1.73m²	71±22	72±16	70±12	0.81	76±21	80±20	79±21	<0.001	79±22	82±25	78±21	0.094
Presentation of unstable CAD												0.006
Unstable angina	0	0	0		0	0	0		256 (50.3)	229 (54.4)	204 (60)	
NSTEMI	0	0	0		0	0	0		128 (50.6)	96 (50)	66 (48.5)	
STEMI	0	0	0		0	0	0		44 (17.4)	54 (28.1)	33 (24.3)	
MI (not classified)	0	0	0		0	0	0		81 (32)	42 (21.9)	37 (27.2)	
Medication use												
Insulin	3 (8.6)	1 (2.2)	3 (4.1)	0.39	80 (11.9)	45 (7)	46 (6.8)	<0.001	40 (7.)	31 (7.4)	23 (6.8)	0.84
Oral antidiabetic	5 (14.3)	2 (4.4)	0 (0.0)	0.004	89 (13.2)	51 (7.9)	54 (8)	<0.001	53 (10.4)	27 (6.4)	21 (6.2)	0.030
ß-Blocker	11 (31.4)	17 (37.8)	27 (37.0)	0.81	434 (64.6)	414 (64.4)	363 (53.9)	<0.001	351 (69)	280 (66.7)	219 (64.4)	0.38
ACE inhibitor	17 (48.6)	19 (42.2)	30 (41.1)	0.76	371 (55)	340 (52.9)	334 (49.6)	0.13	267 (52.5)	203 (48.3)	160 (47.1)	0.25

Calcium antagonist	5 (14.3)	7 (15.6)	11 (15.1)	0.99	130 (19.3)	105 (16.3)	116 (17.2)	0.35	58 (11.4)	39 (9.3)	40 (11.8)	0.47
Diuretic	13 (37.1)	13 (28.9)	15 (20.5)	0.18	231 (34.3)	179 (27.8)	199 (29.6)	0.031	132 (25.9)	110 (26.2)	87 (25.6)	0.98
Statin	6 (17.1)	12 (26.7)	17 (23.3)	0.60	341 (50.6)	325 (50.5)	357 (53)	0.58	184 (36.1)	143 (34)	138 (40.6)	0.17
Acetyl salicylic acid	23 (65.7)	31 (68.9)	46 (63.0)	0.81	575 (85.6)	551 (85.7)	550 (81.7)	0.077	430 (84.5)	354 (84.3)	284 (83.5)	0.93

Legend: Values are numbers (percentages) for categorical data and means ± standard deviations or medians (25^{th}-75^{th} percentiles) for continuous variables; * for differences across the three groups calculated with chi-square test and ANalysis Of VAriance for categorical and continuous data, respectively; † to convert values for total, LDL, HDL, and VLDL cholesterol to millimoles per liter, multiply by 0.02586; to convert values for triglycerides to millimoles per liter, multiply by 0.01129; ‡ ANalysis Of VAriance of logarithmically transformed values

Supplementary table 3

Title: Baseline characteristics according to tertile of HDL cholesterol in ESTHER stratified for CAD

	No CAD				Stable CAD			
	1st tertile	**2nd tertile**	**3rd tertile**	**P***	**1st tertile**	**2nd tertile**	**3rd tertile**	**P***
Number	1546	1665	1728		362	255	182	
Male sex	969 (62.7)	741 (44.5)	404 (23.4)	<0.001	268 (74.1)	148 (58.0)	76 (41.8)	<0.001
Age, years	61.1±6.6	61.7±6.6	61.6±6.6	0.050	64.5±6.2	65.1±5.6	66.6±5.1	<0.001
Body mass index, kg/m²	28.8±4.2	27.8±4.2	26.2±3.9	<0.001	29.0±4.5	28.1±4.5	27.5±4.8	<0.001
Hypertension	891 (57.6)	850 (51.1)	743 (43.0)	<0.001	334 (92.3)	223 (87.5)	147 (80.8)	<0.001
Systolic blood pressure, mmHg	141±19	140±20	138±20	<0.001	141±18	143±19	143±19	0.345
Diastolic blood pressure, mmHg	85±11	84±10	83±11	<0.001	82±10	84±11	84±9	0.087
Diabetes mellitus	302 (19.6)	208 (12.5)	117 (6.8)	<0.001	138 (38.2)	72 (28.2)	36 (19.8)	<0.001
Smoking				<0.001				0.008
Never	637 (42.1)	863 (52.9)	1025 (60.7)		126 (36.2)	116 (46.6)	92 (52.0)	
Former smoker	557 (36.8)	524 (32.1)	454 (26.9)		163 (46.8)	99 (39.8)	65 (36.7)	
Current smoker	318 (21.0)	244 (15.0)	209 (12.4)		59 (17.0)	34 (13.7)	20 (11.3)	
Lipids‡								
Total cholesterol, mg/dl	214±52	224±48	234±50	<0.001	200±54	217±51	218±47	<0.001
LDL cholesterol, mg/dl	148±38	151±35	148±36	0.024	137±40	145±42	142±36	0.040
HDL cholesterol, mg/dl	38±6	52±4	71±11	<0.001	37±6	52±4	69±9	<0.001
Triglycerides, mg/dl	149 (107-220)	115 (81-157)	89 (66-121)	<0.001	142 (101-211)	115 (84-164)	87 (68-115)	<0.001
GFR, ml/min/1.73m²	90±40	87±33	87±34	0.019	88±39	83±30	84±34	0.176
Peripheral vascular disease	12 (0.8)	18 (1.1)	20 (1.2)	0.521	17 (4.8)	11 (4.4)	4 (2.2)	0.344
Cerebrovascular disease	57 (3.8)	37 (2.3)	27 (1.6)	<0.001	31 (9.0)	15 (6.2)	16 (9.2)	0.402
Medication use								
Insulin	47 (3.0)	21 (1.3)	17 (1.0)	<0.001	24 (6.6)	14 (5.5)	6 (3.3)	0.275
Oral antidiabetic	134 (8.7)	68 (4.1)	29 (1.7)	<0.001	54 (14.9)	22 (8.6)	13 (7.1)	0.008
ß-Blocker	341 (22.1)	321 (19.3)	248 (14.4)	<0.001	170 (50.0)	119 (46.7)	60 (33.0)	0.004
ACE inhibitor	351 (22.7)	298 (17.9)	247 (14.3)	<0.001	167 (46.1)	101 (39.6)	77 (42.3)	0.263
Calcium antagonist	163 (10.5)	140 (8.4)	140 (8.1)	0.031	107 (29.6)	65 (25.5)	57 (31.3)	0.363
Diuretic	110 (7.1)	112 (6.7)	87 (5.0)	0.031	86 (23.8)	54 (21.2)	38 (20.9)	0.657

Statin	158 (10.2)	132 (7.9)	157 (9.1)	0.077	136 (37.6)	96 (37.7)	45 (24.7)	0.006
Acetyl salicylic acid	119 (7.7)	114 (6.9)	94 (5.4)	0.031	161 (44.5)	97 (38.0)	59 (32.4)	0.021

Legend: Values are numbers (percentages) for categorical data and means ± standard deviations or medians (25^{th}-75^{th} percentiles) for continuous variables; * for differences across the three groups calculated with chi-square test and ANalysis Of VAriance for categorical and continuous data, respectively; ‡ to convert values for total, LDL, HDL, and VLDL cholesterol to millimoles per liter, multiply by 0.02586; to convert values for triglycerides to millimoles per liter, multiply by 0.01129; § ANalysis Of VAriance of logarithmically transformed values