Association Between Very Low Levels of High-Density Lipoprotein Cholesterol and Long-term Outcomes of Patients With Acute Coronary Syndrome Treated Without Revascularization: Insights From the TRILOGY ACS Trial

Emil Hagström, MD, PhD; Matthew T. Roe, MD, MHS; Gail Hafley, MS; Megan L. Neely, PhD; Mandeep S. Sidhu, MD, MBA; Kenneth J. Winters, MD; Dorairaj Prabhakaran, MD, DM, MSc; Harvey D. White, MB, ChB, DSc; Paul W. Armstrong, MD; Keith A.A. Fox, MB, ChB; E. Magnus Ohman, MD; William E. Boden, MD; for the TRILOGY ACS Investigators

Department of Medical Sciences (Hagström), Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden; Division of Cardiovascular Medicine (Roe, Ohman), Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina; Department of Statistics (Hafley, Neely), Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina; Department of Medicine (Sidhu, Boden), Albany Stratton VA Medical Center and Albany Medical Center, Albany Medical College, Albany, New York; Eli Lilly and Company (Winters), Indianapolis, Indiana; Centre for Chronic Disease Control and Public Health Foundation of India (Prabhakaran), New Delhi, India; Green Lane Cardiovascular Service (White), Auckland City Hospital, Auckland, New Zealand; Division of Cardiology, Department of Medicine/Canadian VIGOUR Centre (Armstrong), University of Alberta, Edmonton, Alberta, Canada; Centre for Cardiovascular Science (Fox), University of Edinburgh, Edinburgh, Scotland, United Kingdom

ABSTRACT

Background: Low levels of high-density lipoprotein cholesterol (HDL-C; <40 mg/dL) are associated with increased risk of cardiovascular events, but it is unclear whether lower thresholds (<30 mg/dL) are associated with increased hazard.

Hypothesis: Very low levels of HDL-C may provide prognostic information in acute coronary syndrome (ACS) patients treated medically without revascularization.

Methods: We examined data from 9064/9326 ACS patients enrolled in the TRILOGY ACS trial. Participants were randomized to clopidogrel or prasugrel plus aspirin. Study treatments continued for 6 to 30 months. Relationships between baseline HDL-C and the composite of cardiovascular death, myocardial infarction (MI), or stroke, and individual endpoints of death (cardiovascular and all-cause), MI, and stroke, adjusted for baseline characteristics through 30 months, were analyzed. The HDL-C was evaluated as a dichotomous variable — very low (<30 mg/dL) vs higher (≥30 mg/dL) — and continuously.

Results: Median baseline HDL-C was 42 mg/dL (interquartile range, 34–49 mg/dL) with little variation over time. Frequency of the composite endpoint was similar for very low vs higher baseline HDL-C, with no risk difference between groups (hazard ratio [HR]: 1.13, 95% confidence interval [CI]: 0.95–1.34). Similar findings were seen for MI and stroke. However, risks for cardiovascular (HR: 1.42, 95% CI: 1.13–1.78) and all-cause death (HR: 1.36, 95% CI: 1.11–1.67) were higher in patients with very low baseline HDL-C.

Conclusions: Medically managed ACS patients with very low baseline HDL-C levels have higher risk of long-term cardiovascular and all-cause death but similar risks for nonfatal ischemic outcomes vs patients with higher baseline HDL-C.

The TRILOGY ACS study was funded by Daiichi Sankyo and Eli Lilly. An employee of Eli Lilly (Dr. Winters) participated as an author on this manuscript. The sponsors had no other role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

E. Hagström reports consulting for Sanofi-Aventis and Ariad and research funding from Amgen, Sanofi-Aventis, GlaxoSmithKline, and AstraZeneca. M.T. Roe reports research grants from Eli Lilly, Daiichi Sankyo, Ferring Pharmaceuticals, Janssen Pharmaceuticals, KAI Pharmaceuticals, the Familial Hypercholesterolemia Foundation, and Sanofi-Aventis; and consulting payments or honoraria from AstraZeneca, Eli Lilly, Merck, Janssen, Elsevier Publishers, Amgen, Bristol-Myers Squibb, Boehringer Ingelheim, PriMed, and Regeneron. All conflicts of interest are listed at <https://www.dcri.org/about-us/conflict-of-interest>. G. Hafley, M.L. Neely, and M.S. Sidhu report no conflicts to disclose. K.J. Winters is an employee and minor stockholder of Eli Lilly. D. Prabhakaran has received research grants from Lilly Foundation and the Medtronic Foundation, and honoraria from Eli Lilly. H.D. White has received grants from Sanofi-Aventis, Lilly, The Medicines Company, the National Institutes of Health, Pfizer, Roche, Johnson & Johnson, Schering-Plough, Merck Sharp & Dohme, AstraZeneca, GlaxoSmithKline, Daiichi Sankyo, and Bristol-Myers Squibb, and is a board member for Merck Sharp & Dohme and Regado Biosciences. P.W. Armstrong reports consulting for Merck, Merck & Co. Inc., Lilly, and GlaxoSmithKline; grants from Boehringer Ingelheim, Hoffmann-La Roche and Sanofi-Aventis Canada Inc. in conjunction with Leuven Coordinating Centre, Amylin in conjunction with Duke Clinical Research Institute, Regado Biosciences, Merck, GlaxoSmithKline, and AstraZeneca in conjunction with Uppsala Clinical Research Centre; and other financial benefit from AstraZeneca and Lilly. K.A.A. Fox has received research grants from AstraZeneca and the British Heart Foundation. E.M. Ohman reports consulting for Abiomed, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Liposcience, Merck, Pozen, Hoffmann-La Roche, Sanofi-Aventis, The Medicines Company, and WebMD; grants from Daiichi Sankyo, Lilly, and Gilead; lecture fees from Gilead Sciences, Boehringer Ingelheim, and The Medicines Company; and travel for Daiichi Sankyo and Lilly. W.E. Boden has received research grant support from AbbVie (AIM-HIGH Trial); reports consulting for AbbVie, Amgen, Arisaph, CardioDx, Gilead, Janssen, Merck, and Sanofi; travel for Eli Lilly; and lecture fees from Abbott Laboratories, Gilead Sciences, Janssen, and Merck.

The authors have no other funding, financial relationships, or conflicts of interest to disclose.

Additional Supporting Information may be found in the online version of this article.

Introduction

Low baseline levels of high-density lipoprotein cholesterol (HDL-C) are a key criterion for metabolic syndrome (MetS), which is associated with increased risk for cardiovascular disease (CVD).¹ Epidemiological data show that low HDL-C is inversely and independently predictive of higher incident rates of cardiovascular events in patients without coronary artery disease (CAD).^{2–4} In patients with stable CAD and in those receiving intensive lipid-lowering therapy, lower HDL-C predicted cardiovascular outcomes.^{5,6} It also is frequently observed in patients with acute coronary syndrome (ACS) upon hospital admission and is associated with increased prevalence of cardiovascular risk factors and more extensive CAD burden upon angiography.^{7–9} In addition, ACS patients with lower HDL-C have a higher risk of short- and long-term morbidity and mortality.^{7,10–13} Recent data from patients with stable CAD and from ACS patients suggest that very low HDL-C (<30 mg/dL [<0.78 mmol/L]) is associated with greatest risk for subsequent cardiovascular events.^{5,7,10} Although low baseline HDL-C is associated with increased risk of post-ACS death,^{7,10} the relationship between very low HDL-C and cardiovascular outcomes in high-risk, medically managed ACS patients remains uncertain. We evaluated risks of long-term cardiovascular outcomes associated with baseline and serial measurements of HDL-C in a large cohort of high-risk, medically managed ACS patients from the randomized Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial.

Methods

Study Design and Subjects

The present post-hoc study was a secondary analysis conducted in the TRILOGY ACS (NCT00699998) trial database of 9326 patients presenting with unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI). Study participants were enrolled from June 2008 to September 2011 in 8 geographic regions comprising 52 countries. The design and primary results of TRILOGY ACS have been previously published.^{14,15} Briefly, patients with UA/NSTEMI were eligible for enrollment if they planned to undergo a treatment strategy of medical management without coronary revascularization within 10 days of the index event and met ≥ 1 of 4 risk criteria (age ≥ 60 years, diabetes mellitus [DM], previous myocardial infarction [MI], or previous revascularization with percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]). Consenting study participants were randomly assigned to receive either clopidogrel (75 mg/d) or prasugrel (10 mg/d; 5 mg/d for patients age ≥ 75 years and/or body weight < 60 kg). All patients received aspirin; a dose of ≤ 100 mg/d was recommended. Study treatments continued for a minimum of 6 months and a maximum of 30 months.

The TRILOGY ACS trial was performed in accordance with the Declaration of Helsinki and was approved by regulatory authorities in all participating countries and by participating sites' institutional review boards. All participants provided written informed consent.

Baseline characteristics, cardiovascular risk factors, medical history, concomitant medications, demographics, and clinical data were recorded. Repeated venous blood sampling of nonfasting serum HDL-C was performed in patients at baseline, at 30 days, and at 6, 12, 18, 24, and 30 months. The study sample consisted of 9064 patients (97.2%; total cohort = 9326) who had valid baseline HDL-C measurements. Data on statin treatment are presented in Table 1, and during the study, 135 patients were treated with ezetimibe at some time point.

The primary efficacy endpoint was the composite of cardiovascular death, nonfatal MI, or nonfatal stroke through 30 months of follow-up. Secondary endpoints were the components of cardiovascular and all-cause death, MI, and stroke.

Statistical Analysis

Baseline characteristics are presented for the 4 groups defined by baseline HDL-C levels. The HDL-C cutpoints used to stratify patients into 4 subgroups were selected based on data derived from recent observational and randomized studies in addition to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines: very low HDL (<30 mg/dL), low HDL (30–39 mg/dL), normal HDL (40–59 mg/dL), and high HDL (≥ 60 mg/dL).^{5,10,16} Continuous variables are presented as medians (interquartile ranges); categorical variables are presented as frequencies (percentages). Differences across the 4 subgroups were assessed using the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables.

To describe the population-level variation in HDL-C levels over time, box plots by treatment were produced showing the following time points: baseline, 30 days, and 6, 12, 18, 24, and 30 months. To examine within-patient variation, spaghetti plots of HDL-C were produced for a random sample of 60 patients. Cumulative distribution graphs by treatment group were examined for the effect of sex, DM, and smoking status on HDL-C levels.

Cumulative event rates for clinical outcomes were calculated using the Kaplan-Meier method and displayed graphically. The outcome differences among the 4 subgroups of HDL-C were assessed statistically using the log-rank test. The effect of baseline HDL-C level (modeled both categorically and continuously) on clinical outcomes was assessed using the Cox proportional hazards model, both unadjusted and adjusted, for baseline risk factors in the TRILOGY adjustment model (including randomized treatment, demographics, baseline clinical characteristics, baseline laboratory values, and concomitant medications; for a list of all variables, see Supporting Information, Table, in the online version of this article).¹⁷ Hazard ratios (HRs) and 95% confidence intervals (CIs) are presented for subsets of very low HDL-C vs higher HDL-C subgroups and for a 5-mg/dL decrease in HDL-C when modeled continuously. In addition, the interaction between baseline HDL-C levels and randomized treatment assignment was assessed both continuously and categorically in the adjusted models.

Restricted cubic spline transformations of HDL-C were used to characterize the relationship of HDL-C to

Table 1. Baseline Characteristics According to HDL-C Categories

	HDL-C Category				P Value
	Very Low (<30 mg/dL), n = 1070	Low ($30\text{--}39$ mg/dL), n = 3085	Normal ($40\text{--}59$ mg/dL), n = 4168	High (≥ 60 mg/dL), n = 741	
Demographics					
Female sex	226 (21.1)	927 (30.0)	1908 (45.8)	495 (66.8)	<0.001
Age, y, median (IQR)	63.0 (55.0–71.0)	64.0 (57.0–72.0)	67.0 (60.0–75.0)	68.0 (62.0–76.0)	<0.001
Age ≥ 75 y	179 (16.7)	582 (18.9)	1043 (25.0)	223 (30.1)	<0.001
Weight, kg, median (IQR)	80.0 (68.0–92.4)	78.0 (67.3–90.0)	74.0 (63.5–84.0)	67.0 (59.0–78.0)	<0.001
Weight <60 kg	128 (12.0)	347 (11.3)	689 (16.5)	204 (27.6)	<0.001
BMI, kg/m ² , median (IQR)	27.7 (24.8–31.2)	27.6 (24.7–31.1)	26.8 (24.1–30.1)	25.3 (22.6–28.6)	<0.001
CV risk factors					
Family history of CAD	303 (32.1)	881 (32.3)	1082 (29.0)	183 (27.7)	0.011
HTN	825 (77.5)	2543 (82.6)	3455 (83.0)	590 (79.8)	<0.001
Hyperlipidemia	603 (59.4)	1774 (60.5)	2297 (57.9)	416 (59.7)	0.182
DM	505 (47.4)	1394 (45.2)	1357 (32.6)	181 (24.5)	<0.001
Current/recent smoking	292 (27.6)	679 (22.2)	711 (17.2)	104 (14.1)	<0.001
Presentation characteristics					
Killip class II–IV	166 (15.5)	374 (12.1)	474 (11.4)	94 (12.7)	0.003
Disease classification					<0.001
UA	269 (25.1)	863 (28.0)	1352 (32.4)	256 (34.5)	
NSTEMI	801 (74.9)	2222 (72.0)	2816 (67.6)	485 (65.5)	
Medical history					
Prior MI	524 (49.3)	1422 (46.5)	1684 (40.7)	256 (34.9)	<0.001
Prior PCI	300 (28.2)	811 (26.5)	1077 (26.0)	166 (22.5)	0.058
Prior CABG	204 (19.2)	554 (18.0)	561 (13.5)	79 (10.7)	<0.001
Prior PAD	90 (8.6)	263 (8.7)	261 (6.3)	47 (6.5)	<0.001
Prior HF	187 (17.6)	530 (17.3)	747 (18.0)	128 (17.5)	0.892
Prior AF	67 (6.4)	197 (6.6)	337 (8.3)	76 (10.5)	<0.001
GRACE risk score, median (IQR)	118 (102–137)	120 (103–138)	122 (106–140)	124 (108–142)	<0.001
Baseline laboratory values, median (IQR)					
Hemoglobin, g/dL	13.6 (12.3–14.7)	13.6 (12.5–14.8)	13.6 (12.5–14.6)	13.2 (12.2–14.1)	<0.001
CrCl, mL/min ^a	78.5 (55.6–106)	75.9 (56.3–101)	71.2 (53.2–92.5)	64.1 (49.7–83.3)	<0.001
LDL-C, mg/dL	77.0 (59.0–101)	85.0 (66.0–110)	91.0 (70–117)	94.0 (73–120)	<0.001
Triglycerides, mg/dL	187 (129–270)	159 (118–220)	135 (103–179)	107 (86–141)	<0.001
Prerandomization investigation					
Angiography performed	456 (42.6)	1294 (41.9)	1675 (40.2)	293 (39.5)	0.253
Concomitant medications					
ASA, daily dose:					

Table 1. Continued

	HDL-C Category				P Value
	Very Low (<30 mg/dL), n = 1070	Low ($30\text{--}39$ mg/dL), n = 3085	Normal ($40\text{--}59$ mg/dL), n = 4168	High (≥ 60 mg/dL), n = 741	
<100 mg	336 (31.4)	1010 (32.7)	1392 (33.4)	294 (39.7)	0.001
100–250 mg	580 (54.2)	1634 (53.0)	2263 (54.3)	347 (46.8)	0.002
>250 mg	93 (8.7)	262 (8.5)	246 (5.9)	49 (6.6)	<0.001
β -Blocker	854 (79.8)	2449 (79.4)	3211 (77.0)	548 (74.0)	0.002
ACEI/ARB	797 (74.5)	2384 (77.3)	3131 (75.1)	519 (70.0)	<0.001
Statin	899 (84.0)	2630 (85.3)	3442 (82.6)	598 (80.7)	0.003
PPI	281 (26.3)	768 (24.9)	1018 (24.4)	204 (27.5)	0.243

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ASA, aspirin; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CrCl, creatinine clearance; CV, cardiovascular; DM, diabetes mellitus; GRACE, Global Registry of Acute Coronary Events; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HTN, hypertension; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; UA, unstable angina.

Values are expressed as n (%) unless otherwise indicated.

To convert values for HDL-C to mmol/L, multiply by 0.02586.

^aCrCl calculated using Cockcroft-Gault formula.

the endpoint and to test for linearity. Predicted event rates at 30 months (y-axis) were plotted by baseline HDL-C level (x-axis) using Cox proportional hazards regression modeling. Significant nonlinear relationships were addressed appropriately in the Cox proportional hazards models.

P values <0.05 from 2-sided tests were considered statistically significant. All analyses were performed independently at the Duke Clinical Research Institute, Duke University, Durham, North Carolina, using SAS version 9.2 (SAS Institute Inc., Cary, NC).

Results

Baseline characteristics for study participants according to the HDL-C categories are shown in Table 1. The median baseline HDL-C level for the overall study population was 42 mg/dL (34–49 mg/dL, 1.09 mmol/L [95% CI: 0.88–1.3]). Of the 9064 patients included in this study, 1070 (12%) had very low HDL-C (<30 mg/dL) baseline values; 3085 (34%) had low HDL-C (30–39 mg/dL) baseline values; 4168 (46%) had normal HDL-C (40–59 mg/dL) baseline values; and 741 (8%) had high baseline HDL-C (≥ 60 mg/dL) baseline values. Compared with patients who had higher HDL-C levels, those with very low HDL-C levels were younger; more likely to be male, present with NSTEMI, and be current smokers, and more frequently had DM, prior MI, prior CABG surgery, and prior peripheral arterial disease. Additionally, these patients were more likely to have lower baseline levels of low-density lipoprotein cholesterol (LDL-C) and higher triglyceride (TG) levels (Table 1). During follow-up study visits, HDL-C levels were stable in the overall population and also by randomized treatment assignment (see Supporting Information, Figure, in the online version of this article). The intra-individual variation in HDL-C levels among a randomly selected group of patients was also small and stable over

time. No differences in HDL-C distribution by randomized treatment were detected for sex, DM, or smoking status (data not shown).

The unadjusted frequency of the composite endpoint of cardiovascular death, MI, or stroke through 30 months was similar across the 4 baseline HDL-C categories (Table 2). Similar findings were observed for both MI and stroke as individual component endpoints. The unadjusted frequencies of cardiovascular death and all-cause death were highest in the subset of patients with very low HDL-C levels, with a significant difference across the 4 subgroups. The distributions of event curves through 30 months across HDL-C categories were similar for the composite endpoint, MI, and stroke (Figure 1A–C). However, event curves for the subset of patients with very low HDL-C levels separated early from the other 3 HDL-C subsets for both cardiovascular death and all-cause death, with a higher risk demonstrated through 30 months (Figure 1D,E). The continuous relationship between baseline HDL-C levels and the unadjusted risk of cardiovascular death and all-cause death at 30 months demonstrated a linear increase for HDL-C levels <30 mg/dL (Figure 2A,B).

Importantly, in adjusted Cox proportional hazards models, very low vs higher HDL-C levels were associated with a moderately increased risk of cardiovascular death (adjusted HR: 1.42, 95% CI: 1.13–1.78) and all-cause death (adjusted HR: 1.36, 95% CI: 1.011–1.67); however, this association was not seen with the composite endpoint, MI, or stroke (Table 3). Similar findings were demonstrated for lower HDL-C values, when HDL-C was modeled as a continuous variable, but significant findings for all-cause death were only observed in the category of patients with very low HDL-C levels (<30 mg/dL).

There was no evidence of treatment interaction (prasugrel vs clopidogrel) by very low vs higher HDL-C categories

Table 2. Unadjusted Event Rates According to Clinical Baseline HDL-C Categories

	HDL-C Category				Log-Rank <i>P</i> Value
	Very Low (<30 mg/dL), <i>n</i> = 1070	Low ($30\text{--}39$ mg/dL), <i>n</i> = 3085	Normal ($40\text{--}59$ mg/dL), <i>n</i> = 4168	High (≥ 60 mg/dL), <i>n</i> = 741	
CV death, MI, or stroke	171	452	522	96	0.0622
Event rate at 30 mo (95% CI)	21.9 (18–26)	20.8 (19–23)	17.7 (16–20)	20.7 (16–26)	
CV death	103	223	257	46	0.0058
Event rate at 30 mo (95% CI)	12.6 (10–15)	10.8 (9.2–12)	8.9 (7.6–10)	11.0 (6.3–16)	
MI	100	266	298	57	0.1037
Event rate at 30 mo (95% CI)	13.7 (9.5–18)	12.4 (11–14)	10.3 (8.9–12)	11.7 (8.3–15)	
Stroke	13	40	62	11	0.7397
Event rate at 30 mo (95% CI)	1.8 (0.7–2.9)	2.1 (1.3–2.9)	2.4 (1.7–3.1)	3.8 (0.0–7.8)	
All-cause death	126	268	325	60	0.0064
Event rate at 30 mo (95% CI)	14.9 (12–18)	12.3 (11–14)	10.9 (9.6–12)	12.9 (8.6–17)	

Abbreviations: CI, confidence interval; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction.
Table displays the cumulative number of events up to 30 mo followed by Kaplan-Meier event rates at 30 mo in percentage values with 95% CIs.

or for continuous HDL-C measurements in the adjusted models for the composite endpoint (binary, $P=0.951$; continuous, $P=0.165$) or for all-cause death (binary, $P=0.600$; continuous, $P=0.052$).

Discussion

In this large contemporary trial of medically managed ACS patients followed over 30 months, very low levels of HDL-C (<30 mg/dL [<0.78 mmol/L]) and continuously lower levels of HDL-C were independently associated with increased rates of cardiovascular death and all-cause death, but we did not detect an association between baseline HDL-C levels and frequency of the composite endpoint or the nonfatal ischemic component endpoints of MI or stroke. Levels of HDL-C were stable both intra- and interindividually over time, in contrast with other lipid variables in the post-ACS setting. Finally, we observed no differences in the relationship between assigned study treatment (prasugrel vs clopidogrel) and outcomes as a function of baseline HDL-C level. In this trial, no difference in treatment effect comparing prasugrel with clopidogrel on the primary composite endpoint was detected, as previously reported.

Our results are in accord with the consistent inverse associations observed between baseline HDL-C levels and both cardiovascular and all-cause death in the general population.^{2–4,18} In addition, our data showing that ACS patients with very low levels of HDL-C had significantly increased cardiovascular death and all-cause mortality are consistent with other recent post-hoc data from randomized trials and observational studies, which indicate that the threshold of HDL-C <30 mg/dL may be a particularly important discriminator of increased hazard, particularly fatal outcomes. In accordance with our data, patients with recent ACS or verified CAD with the lowest tertile of the HDL₃-C subclass had increased risk for ischemic events

and mortality during follow-up.¹⁸ Further, the HDL-C particle size assessed by HDL-C/apolipoprotein A1 ratio has been shown to be predictive of myocardial damage estimated by troponin elevation after percutaneous coronary revascularization.¹⁹ This is also consistent with the overall differentially increased risk of profile such patients with very low HDL-C levels exhibited in our study and other studies.^{5–7,10,12} Furthermore, patients with stable CAD who have low HDL-C levels have been shown to have an increased burden of cardiovascular risk factors and more severe CAD upon angiography.^{7–10} Additional reports have shown that lower HDL-C levels are associated with increased risk of major adverse cardiovascular events and death in patients receiving both guideline-based revascularization¹³ and in those receiving statin therapy. Although some data suggest that the prognostic value of HDL-C levels relative to outcomes is mitigated among patients receiving statin treatment who achieve low LDL-C levels,^{5,6,20–22} a recent post-hoc analysis in stable CAD patients demonstrated that the prognostic importance of HDL-C levels <30 mg/dL in predicting higher rates of death or MI during long-term follow-up persisted among the subset of patients who achieved and maintained an on-treatment LDL-C level of <70 mg/dL on statin therapy, even after adjustment for relevant covariates.⁵

Several mechanisms may potentially explain the association between low HDL-C levels and the subsequent risk of clinical events. Preclinical and clinical studies suggest that higher levels of HDL-C reduce vascular disease progression via antithrombotic, antioxidant, and anti-inflammatory properties, as well as through increased reverse cholesterol transport of LDL-C; while, conversely, lower levels of HDL-C may be associated with a proatherogenic milieu.^{6,23,24} Lower levels of HDL-C (and particularly very low levels) have been associated with a wide range of comorbidities and risk factors (eg, DM, smoking, prior CVD) that may be directly

Figure 1. Kaplan-Meier event curve by clinical baseline HDL-C levels for the primary composite endpoint of (A) cardiovascular death, MI, or stroke; (B) MI; (C) stroke; (D) cardiovascular death; and (E) all-cause death during 30 months of follow-up. Abbreviations: HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction.

Figure 2. Continuous unadjusted relationship between HDL-C (mg/dL) values and (A) cardiovascular death and (B) all-cause death. Solid lines show predicted event rate at 30 months (with 95% CIs, dashed lines) in relation to HDL-C as a function of a restricted cubic regression spline. Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol.

or indirectly related to an increase in CVD and death. Low baseline levels of HDL-C may, therefore, reflect a subset of individuals with a longer accumulated exposure to cardiovascular risk factors and more extensive atherosclerotic

disease. Furthermore, because low HDL-C is a key component of MetS—a somewhat controversial cluster of risk factors that also includes insulin resistance, obesity, hypertension, and hypertriglyceridemia—our results may simply reflect the influence of these individual component risk factors rather than the direct effect of low HDL-C levels per se on the progression of vascular disease.²⁵ The possible causal association between levels of HDL-C and CAD is substantiated in a Mendelian randomization study indicating a protective effect for higher HDL-C.²⁶ Moreover, the inverse association observed between HDL-C <30 mg/dL and cardiovascular and all-cause death (but not MI and stroke) may indicate that such very low HDL-C levels are related to, or more closely reflect, overall atherosclerosis burden and associated plaque vulnerability, rather than a prothrombotic milieu, such that these more vulnerable plaques may be more at risk for rupture and possibly fatal events such as sudden cardiac death. Unfortunately, we were unable to assess whether the deaths observed in TRILOGY ACS were sudden arrhythmic deaths or due to other cardiovascular causes. In addition, because lower HDL-C levels are closely associated with other atherogenic components of lipoprotein metabolism, it is possible that lower levels of HDL-C are a marker for other lipoprotein metabolism abnormalities, such as higher levels of TG or atherogenic remnant lipoproteins or a higher proportion of small, dense LDL-C predisposing to a higher risk of cardiovascular and all-cause mortality.^{27,28}

Several prior trials have investigated the possible benefit of raising HDL-C levels; however, results to date have been largely neutral or negative. In the dal-OUTCOMES trial, the cholesteryl ester transfer protein (CETP) inhibitor dalcetrapib increased HDL-C levels by as much as 40% with no reduction in the incidence of cardiovascular outcomes in patients with recent ACS, although these patients were not preselected for having low levels of baseline HDL-C.²⁹ Findings from the earlier Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) trial of the CETP inhibitor torcetrapib in high-risk ACS patients with CVD likewise showed a 72% increase in HDL-C levels.

Table 3. Risk of Outcomes in Very Low vs Higher HDL-C and per 5-mg/dL Decrease in HDL-C

	HDL-C <30 vs ≥30 mg/dL		5-mg/dL Decrease in HDL-C	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
CV death, MI, or stroke	1.16 (0.99-1.36)	1.13 (0.95-1.34)	1.02 (1.00-1.05)	1.02 (0.99-1.05)
CV death	1.42 (1.15-1.75)	1.42 (1.13-1.78)	1.05 (1.01-1.08)	1.04 (1.00-1.08)
MI	1.17 (0.95-1.45)	1.14 (0.92-1.43)	1.03 (0.99-1.06)	1.02 (0.98-1.05)
Stroke	0.83 (0.47-1.47)	0.91 (0.49-1.66)	0.98 (0.91-1.05)	0.99 (0.92-1.08)
All-cause death	1.39 (1.15-1.68)	1.36 (1.11-1.67)	—	—
Per 5-mg/dL decrease for HDL-C <30 mg/dL	—	—	1.30 (1.21-1.50)	1.18 (1.02-1.36)
Per 5-mg/dL decrease for HDL-C ≥30 mg/dL	—	—	1.01 (0.98-1.05)	1.02 (0.98-1.06)

Abbreviations: CI, confidence interval; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; MI, myocardial infarction. Data are from Cox proportional hazards models.

However, the trial was terminated early due to a higher risk of mortality in the active-treatment group that was subsequently determined to be caused by unexpected off-target drug effects.³⁰ As in the dal-OUTCOMES trial, patients in the ILLUMINATE trial were not preselected on the basis of HDL-C profiling at baseline. Currently, the Randomized Evaluation of the Effects of Anacetrapib Through Lipid Modification (REVEAL; NCT01252953) and A Study of Evacetrapib in High-Risk Vascular Disease (ACCELERATE; NCT01687998) trials are investigating the CETP inhibitors anacetrapib and evacetrapib, respectively, in patients with stable CAD, but these trials are still underway.

In the Atherothrombosis Intervention in Metabolic Syndrome With Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) trial, patients with CVD and well-controlled LDL levels who were preselected with low baseline levels of HDL-C (<40 mg/dL for men; <50 mg/dL for women) showed no additional clinical benefit of extended-release niacin treatment added to a background of LDL-C reduction therapy (simvastatin ± ezetimibe), despite a significant 25% increase in HDL-C levels with this treatment.³¹ Although an exploratory subgroup analysis of AIM-HIGH suggested a trend toward clinical benefit with niacin in a subset of patients with both low HDL-C levels (<32 mg/dL) and elevated TG (>200 mg/dL), such post-hoc findings should be viewed cautiously as hypothesis-generating only.³² Similar data have recently been reported from the HPS2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial for patients with vascular disease treated with simvastatin, where the addition of an extended-release niacin combined with the prostaglandin inhibitor laropiprant did not reduce the risk of major vascular events, but instead increased the risk of serious adverse events such as DM development and disturbed DM control despite large increases in HDL-C levels.³³ As noted above, other than AIM-HIGH, all trials to date of HDL-C-raising therapies have included broad populations of patients with CVD regardless of baseline HDL-C levels. Adequately sized trials targeted to populations of patients with very low levels of baseline HDL-C, who are presumed to be at highest risk for subsequent cardiovascular events, are thus needed to determine whether therapies would selectively benefit such patients and reduce residual risk.

Study Limitations

Our analysis has several limitations. First, TRILOGY ACS included only patients with medically managed ACS, and caution should be exercised in generalizing our findings to other ACS populations, such as those undergoing revascularization. Second, the prespecified HDL-C categories were based upon clinically accepted categories of HDL-C ranges that have been shown in recent studies to be predictive of clinical events^{5,7,10}; nevertheless, this may introduce a certain imprecision in the analyses of how very low levels of HDL-C may impact clinical outcomes. However, we also evaluated HDL-C as a continuous variable and demonstrated similar findings. Third, because variables

included in the MetS, such as fasting blood glucose and waist circumference, were not collected, we were unable to relate HDL-C to other constituent variables that constitute the MetS cluster. Fourth, the baseline for this study was time of randomization and the results may reflect acute-phase alterations of HDL-C levels related to higher inflammatory activity rather than pre-ACS levels. Despite this uncertainty, HDL-C provided robust information on outcomes during follow-up; further, the degree of intra-individual HDL-C variation over time was quite small. Fifth, it is possible that low levels of HDL-C are a marker of general disease, heart failure, prior revascularization, and poor prognosis rather than being involved in disease progression. Lastly, data on statin treatment were recorded and included in the adjustment model; however, no information on type or dose was collected.

Conclusion

Very low levels of HDL-C (<30 mg/dL) were associated with a higher long-term risk of both cardiovascular and all-cause death, but not MI or stroke, in this population of medically managed, high-risk ACS patients. Although the data from this post-hoc analysis is hypothesis-generating and not indicating a causal effect, taken together with other recent data, our findings suggest that an HDL-C threshold of <30 mg/dL may be a better predictor of increased cardiovascular risk than previously defined cutpoints such as <40 mg/dL. Future prospective studies will be required to test whether this more stringent threshold of risk for very low levels of HDL-C provides more robust prognostic information that may guide subsequent secondary prevention interventions aimed at reducing clinical events and residual cardiovascular risk, even among patients who achieve desirable or “optimal” levels of LDL-C on high-potency statin therapy.

Acknowledgments

The authors wish to thank Karen Pieper, MS, for expert coordination and management of the statistical analytic team; Jonathan McCall, MS, for expert editorial assistance; and Kerry Stenke for expert graphics assistance. Ms. Pieper, Mr. McCall, and Ms. Stenke are employees of the Duke Clinical Research Institute, Durham, North Carolina; none received any compensation for their work on this article other than their usual salaries.

References

1. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol*. 2007;49:403–414.
2. Castelli WP, Garrison RJ, Wilson PW, et al. Incidence of coronary heart disease and lipoprotein cholesterol levels: the Framingham Study. *JAMA*. 1986;256:2835–2838.
3. Assmann G, Schulte H, von Eckardstein A, et al. High-density lipoprotein cholesterol as a predictor of coronary heart disease risk: the PROCAM experience and pathophysiological implications for reverse cholesterol transport. *Atherosclerosis*. 1996;124(suppl):S11–S20.
4. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease: four prospective American studies. *Circulation*. 1989;79:8–15.

5. Acharjee S, Boden WE, Hartigan PM, et al. Low levels of high-density lipoprotein cholesterol and increased risk of cardiovascular events in stable ischemic heart disease patients: a post-hoc analysis from the COURAGE Trial. *J Am Coll Cardiol*. 2013;62:1826–1833.
6. Barter P, Gotto AM, LaRosa JC, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med*. 2007;357:1301–1310.
7. Roe MT, Ou FS, Alexander KP, et al. Patterns and prognostic implications of low high-density lipoprotein levels in patients with non-ST-segment elevation acute coronary syndromes. *Eur Heart J*. 2008;29:2480–2488.
8. Sachdeva A, Cannon CP, Deedwania PC, et al. Lipid levels in patients hospitalized with coronary artery disease: an analysis of 136 905 hospitalizations in Get With The Guidelines. *Am Heart J*. 2009;157:111.e2–117.e2.
9. Schaffer A, Verdoia M, Barbieri L, et al. High-density lipoproteins and coronary artery disease: a single-center cohort study. *Angiology*. 2014;65:696–702.
10. Acharjee S, Roe MT, Amsterdam EA, et al. Relation of admission high-density lipoprotein cholesterol level and in-hospital mortality in patients with acute non-ST-segment elevation myocardial infarction (from the National Cardiovascular Data Registry). *Am J Cardiol*. 2013;112:1057–1062.
11. Olsson AG, Schwartz GG, Szarek M, et al. High-density lipoprotein, but not low-density lipoprotein, cholesterol levels influence short-term prognosis after acute coronary syndrome: results from the MIRACL trial. *Eur Heart J*. 2005;26:890–896.
12. Duffy D, Holmes DN, Roe MT, et al. The impact of high-density lipoprotein cholesterol levels on long-term outcomes after non-ST-elevation myocardial infarction. *Am Heart J*. 2012;163:705–713.
13. Wolfram RM, Brewer HB, Xue Z, et al. Impact of low high-density lipoproteins on in-hospital events and one-year clinical outcomes in patients with non-ST-elevation myocardial infarction acute coronary syndrome treated with drug-eluting stent implantation. *Am J Cardiol*. 2006;98:711–717.
14. Roe MT, Armstrong PW, Fox KA, et al; TRILOGY ACS Investigators. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med*. 2012;367:1297–1309.
15. Chin CT, Roe MT, Fox KA, et al; TRILOGY ACS Steering Committee. Study design and rationale of a comparison of prasugrel and clopidogrel in medically managed patients with unstable angina/non-ST-segment elevation myocardial infarction: the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial. *Am Heart J*. 2010;160:16.e1–22.e1.
16. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
17. Roe MT, Goodman SG, Ohman EM, et al. Elderly patients with acute coronary syndromes managed without revascularization: insights into the safety of long-term dual antiplatelet therapy with reduced-dose prasugrel versus standard-dose clopidogrel. *Circulation*. 2013;128:823–833.
18. Martin SS, Khokhar AA, May HT, et al. HDL cholesterol subclasses myocardial infarction and mortality in secondary prevention: the Lipoprotein Investigators Collaborative (LIC). *Eur Heart J*. 2015;36:22–30.
19. Li XL, Li JJ, Guo YL, et al. The ratio of high-density lipoprotein cholesterol to apolipoprotein A-I predicts myocardial injury following elective percutaneous coronary intervention. *Clin Cardiol*. 2014;37:558–565.
20. deGoma EM, Leeper NJ, Heidenreich PA. Clinical significance of high-density lipoprotein cholesterol in patients with low low-density lipoprotein cholesterol. *J Am Coll Cardiol*. 2008;51:49–55.
21. Jafri H, Alsheikh-Ali AA, Karas RH. Meta-analysis: statin therapy does not alter the association between low levels of high-density lipoprotein cholesterol and increased cardiovascular risk. *Ann Intern Med*. 2010;153:800–808.
22. Ridker PM, Genest J, Boekholdt SM, et al; JUPITER Trial Study Group. HDL cholesterol and residual risk of first cardiovascular events after treatment with potent statin therapy: an analysis from the JUPITER trial. *Lancet*. 2010;376:333–339.
23. deGoma EM, deGoma RL, Rader DJ. Beyond high-density lipoprotein cholesterol levels evaluating high-density lipoprotein function as influenced by novel therapeutic approaches. *J Am Coll Cardiol*. 2008;51:2199–2211.
24. Choudhury RP, Rong JX, Trogan E, et al. High-density lipoproteins retard the progression of atherosclerosis and favorably remodel lesions without suppressing indices of inflammation or oxidation. *Arterioscler Thromb Vasc Biol*. 2004;24:1904–1909.
25. Mottillo S, Filion KB, Genest J, et al. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;56:1113–1132.
26. Burgess S, Freitag DF, Khan H, et al. Using multivariable Mendelian randomization to disentangle the causal effects of lipid fractions. *PLoS One*. 2014;9:e108891.
27. Hoogeveen RC, Gaubatz JW, Sun W, et al. Small dense low-density lipoprotein-cholesterol concentrations predict risk for coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study. *Arterioscler Thromb Vasc Biol*. 2014;34:1069–1077.
28. Expert Dyslipidemia Panel of the International Atherosclerosis Society Panel. An International Atherosclerosis Society Position Paper: global recommendations for the management of dyslipidemia—full report. *J Clin Lipidol*. 2014;8:29–60.
29. Schwartz GG, Olsson AG, Abt M, et al; dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;367:2089–2099.
30. Barter PJ, Caulfield M, Eriksson M, et al; ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med*. 2007;357:2109–2122.
31. Boden WE, Probstfield JL, Anderson T, et al; AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy [published correction appears in *N Engl J Med*. 2012;367:189]. *N Engl J Med*. 2011;365:2255–2267.
32. Guyton JR, Slee AE, Anderson T, et al. Relationship of lipoproteins to cardiovascular events: the AIM-HIGH Trial (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes). *J Am Coll Cardiol*. 2013;62:1580–1584.
33. Landray MJ, Haynes R, Hopewell JC, et al; HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med*. 2014;371:203–212.