Effect of High-Density Lipoprotein Cholesterol Levels on Overall Survival and Major Adverse Cardiovascular and Cerebrovascular Events

Manpreet Kaur, MD[a], Keerat Rai Ahuja, MD[a], Shameer Khubber, MD[a], Leon Zhou, MD[a], Beni Rai Verma, MD[a], Chandramohan Meenakshisundaram, MD[a], Mohamed M Gad, MD[a], Anas Saad, MD[a], Kamalpreet Dhaliwal, MD[a], Toshiaki Isogai, MD, MPH[a], Jeevanatham Rajeswaran, PhD[b], Andrew Toth, MS[b], Johnny Chahine, MD[a], Leslie Cho, MD[a], Rishi Puri, MD[a], and Samir Kapadia, MD[a,*]

Several studies designed to augment high density lipoprotein (HDL) levels have so far been unsuccessful in reducing rates of major adverse cardiovascular and cerebrovascular events (MACCE). In this study, we report the effect of HDL-C levels on overall survival outcomes and rates of MACCE following percutaneous coronary intervention (PCI). We reviewed patients who underwent PCI at the Cleveland Clinic from 2005 to 2017 and followed them through the end of 2018. Restricted cubic splines incorporated into Cox proportional hazard regression models were used to assess the outcomes. The HDL-C level associated with the lowest mortality was used as a reference value.15,633 patients underwent PCI during the study period, of which 70% were male, 81% were white, and 73% were on statins. The mean age at the time of procedure was 65.8 ± 11.8 years. After adjusting for demographics, co-morbidities, lipid profile, statin use, and date of procedure, our model demonstrated a U-shaped association between HDL-C and overall mortality, with HDL-C levels of 30-50 mg/dl associated with the most favorable outcomes, and HDL-C levels < 30 mg/dl or > 50 mg/dl associated with worse outcomes. A sensitivity analysis in men yielded a similar U-shaped association. In conclusion, our study shows that both low and high levels of HDL-C are associated with worse overall survival, with no effect on rates of MACCE in PCI patients. Further studies are required to understand the mechanism of this association between elevated HDL-C levels with increased overall mortality in patients with atherosclerotic cardiovascular disease (ASCVD). **(Am J Cardiol 2021;146:8−14)**

High-density lipoproteins (HDLs) are known for their multiple biological functions, having anti-atherogenic, anti-inflammatory, antioxidative, antiapoptotic, and vasodilatory properties.[1,2] Historically, low levels of circulating HDL cholesterol (HDL-C) have been well established as an independent risk predictor for cardiovascular disease. The Framingham Study and other studies have suggested a linear inverse relationship between HDL-C levels, risk of cardiovascular events, and overall mortality.[3-6] However, more recent observational studies have challenged this early hypothesis.[7-9] Multiple studies have shown that HDL particles become dysfunctional at high levels due to alteration in the protein structure, as seen in chronic disease states, acute inflammatory states, and the acute coronary syndrome.[10,11] Large-scale studies assessing for associations of all-cause mortality and MACCE outcomes with HDL-C levels in CAD population (specifically after-PCI) are lacking. To our best knowledge, this is the first study to study CAD patients who have undergone PCI assess the relationship between HDL-C levels and LDL-C levels with and outcomes.

Methods

In accordance with the statement checklist outlined in Strengthening the Reporting of Observational Studies in Epidemiology (STROBE),[12] we conducted a single-center retrospective observational cohort study of the patients who have undergone PCI at our center, from January 2005 through September 2017, with approval from the Institutional Review Board of the Cleveland Clinic Foundation. Patients who had the following labs drawn within one year pre- and after-PCI were included: fasting HDL-C, fasting low-density lipoprotein cholesterol (LDL-C), fasting total cholesterol, and fasting triglycerides. Patients younger than 18 years of age, patients without the necessary laboratory work within the 1-year peri-procedural time frame discussed above, and patients who lost follow-up were excluded. The primary end point was all-cause mortality.

[a]Robert and Suzanne Tomsich Department of Cardiovascular Medicine, Heart, Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, Ohio; and [b]Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, Ohio. Manuscript received September 18, 2020; revised manuscript received and accepted January 13, 2021.

This study was made possible by a generous gift from Jennifer and Robert McNeil. The funders had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, and the preparation, review, or approval of the manuscript.

See page 13 for disclosure information.

*Corresponding author: Tel: (216)-444-6735; fax: (216)445-6176.

E-mail address: kapadis@ccf.org (S. Kapadia).

0002-9149/
https://doi.org/10.1016/j.amjcard.2021.01.014

Secondary outcomes included stroke, myocardial infarction, revascularization, and major adverse cardiovascular and cerebrovascular events (MACCE). MACCE was defined as the composite of stroke, all-cause mortality, myocardial infarction, and revascularization (target lesion revascularization and coronary artery bypass grafting). All patients were followed up by chart review through the electronic medical record system through December 31, 2018. Data were summarized with simple descriptive statistics. Continuous variables were presented with mean ± standard deviation, 15th, 50th (median), and 85th percentiles. Categorical data were described using frequencies and percentages. Time zero for the analysis was the time of PCI. Primary outcomes were analyzed as the time to events. The association of HDL-C to the outcomes was analyzed using Cox proportional hazard regression.[13] One model was fit for the overall cohort, then separate analyses were performed for men and women to see the association of HDL-C with all-cause mortality in these subgroups. Overall survival for the entire cohort was assessed using a parametric multiphase hazard model. The final cause-specific hazard model was adjusted for the following co-variables: age, gender, preoperative body mass index (BMI), race, total cholesterol, triglycerides, LDL-C, and existing co-morbidities (diabetes, hypertension, prior myocardial infarction, peripheral arterial disease, heart failure, cerebrovascular disease, statin use, prior valve surgery, prior coronary artery bypass surgery, prior PCI) mentioned in supplementary materials. We used a Cox proportional-hazard model and divided HDL-C into 7 knots: 2.5th, 18.33rd, 34.17th, 50th, 63.83rd, 81.67th, and 97.5th percentile. HDL-C was also used as a continuous variable from 20 to 100 mg/dl and restricted cubic splines were created. Follow-up of the patients was performed via chart review through the electronic medical record system at our institute. All analyses were performed using the R Foundation for statistical computing (R version 3.5.3; Vienna, Austria) and SAS (version 9.3, SAS Institute Inc., Cary, North Carolina).

Results

From 18,000 patients who underwent PCI during the study period, 15,633 adults met inclusion criteria and were followed through December 31, 2018. The mean age of the patients was 66 years (SD: 12) and 70% were men. Descriptive statistics of the lipid profile and overall cohort for continuous and categorical variables are shown in Table 1.

In the overall cohort, 2,455 patients died during follow-up. a total of 50% of the survivors were followed for more than years, 25% of the survivors were followed for more than 5.6 years, 10% of the survivors were followed 2.4 for more than 8 years, and 5% of the survivors were followed for more than 10 years. After adjusting the co-variables by using splines, a U-shaped curved was found for the association between HDL-C levels and all-cause mortality as shown in Figure 1A. HDL-C values less than 30 mg/dl and greater than 50 mg/dl were associated with an increased risk of mortality. In addition, an association of LDL-C with overall mortality was also noted, with a significantly increased risk of mortality in patients with LDL-C greater than 120 mg/dl (Figure 2). In the male cohort, 1619 patients

Table 1
Descriptive statistics for the overall cohort (categorical and continuous variable)

Variable	Number (N)	Mean ± SD/n (%)
Age (years)	15633	65.8 ± 11.8
Men	15633	10,949(70%)
Women	15633	4684 (30%)
Black	15633	2106 (13%)
White	15633	12687 (81%)
Other	15633	840 (5.4%)
Body Mass Index (kg/m^2)	14959	29.4 ± 6.39
Co-morbidities		
Prior Coronary artery bypass grafting (CABG)	15626	4300 (28%)
Prior Heart Failure	15600	3078 (20%)
Prior Cerebrovascular disease	15629	2725 (17%)
Prior Diabetes	15628	5922 (38%)
Prior Statins	15633	11473 (73%)
Hypertension	15627	13232 (85%)
Prior Myocardial Infarction	15628	5438 (35%)
Prior Peripheral Arterial Disease	15603	2553 (16%)
Prior PCI	15626	5059 (32%)
Prior Valve Surgery	15625	436 (2.8%)
Lipid profile		
Total cholesterol (mg/dl)	15598	163 ± 46.4
Triglycerides (mg/dl)	15588	142 ± 122
Low-density lipoprotein (mg/dl)	15510	91.2 ± 39.3
High density lipoprotein cholesterol (mg/dl)	15633	44.8 ± 13.7

died on follow-up. The median vital status follow-up was 3.7 years (mean ± SD: 4.6 ± 3.9 years). 50% of survivors were followed for more than 2.5 years, 25% of patients followed more than 7.4 years, 10% more than 10.5 years and 5% more than 12 years. A similar U-shaped curve was obtained associating HDL-C levels to mortality (Figure 3). In the female cohort, 836 patients died on follow up. There was a nonsignificant increased risk of mortality, as evidenced by confidence intervals including 1 for HDL-C values (Figure 4).

A total of 4,228 MACCE events were observed on follow-up. There was a slight increase in the adjusted risk for

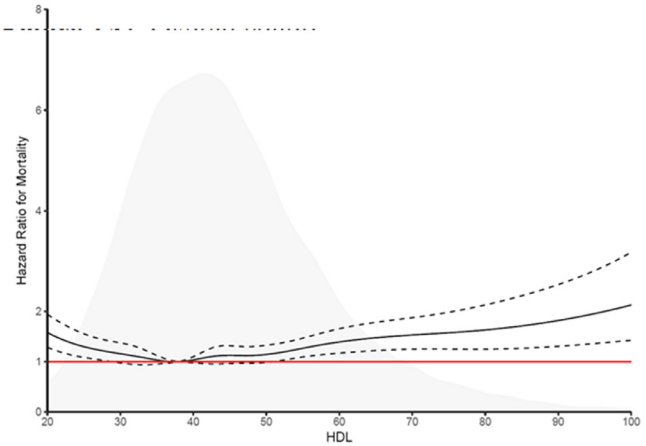

Figure 1A. Overall cohort, HDL on a continuous scale and risk of mortality. Solid Line resents risk-adjusted hazard ratio enclosed by 95% confidence intervals (dashed) from Cox regression using restricted cubic splines. The grey area in the background indicates distribution of HDL.

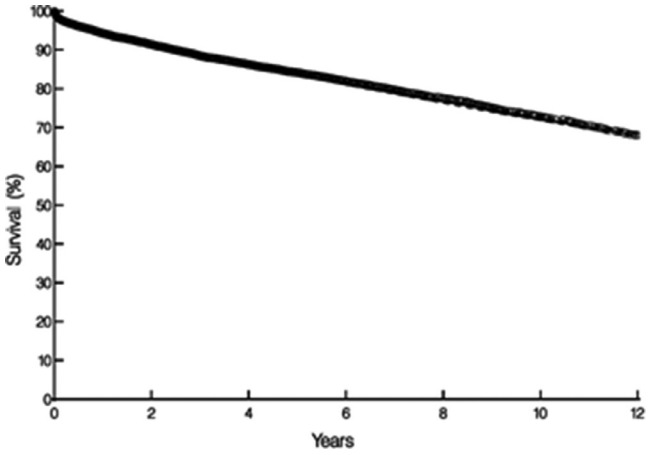

Figure 1B. Observed survival - Overall cohort: Black Line represents parametric estimates of survival for all patients. Dashed lines represent 68% Confidence Intervals. The dots represent nonparametric Kaplan-Meier estimates for survival.

MACCE in patients with low HDL-C levels (25mg/dl), compared with the median (Figure 5A and B). However, higher levels of LDL-C were also associated with a significant increase in the adjusted risk of MACCE (Figure 5C). A total of 1,170 patients suffered from strokes. However, there was no significant increase or decrease in the adjusted incidence of stroke associated with HDL-C levels (Figure 5D). A total of 749 myocardial infarctions (MI) were found on follow-up, but no association of HDL-C level to adjusted rate of MI was seen (Figure 5F and G). On follow-up after PCI, 597 patients were revascularized (Figure 5).

Discussion

This large observational study in after-PCI patients demonstrate a U-shaped association of both low and high HDL-C levels with increased overall mortality. However, this U-shaped curve was observed only in the male cohort and was not noted in the female cohort. An increase in mortality and MACCE outcomes with increasing LDL-C levels was also seen.

Prior literature suggested an inverse and linear relationship between HDL-C levels and overall mortality.[3-6] However, more recently published prospective studies have observed similar U-shaped associations of HDL-C levels

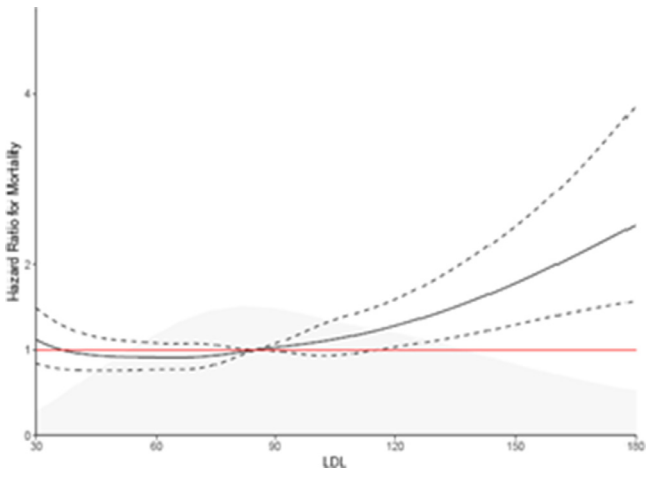

Figure 2. Mortality and LDL - Overall cohort: LDL on a continuous scale and risk of mortality. Solid Line represents risk-adjusted hazard ratio enclosed by 95% confidence intervals (dashed) from Cox regression using restricted cubic splines. The grey area in the background indicates distribution of LDL.

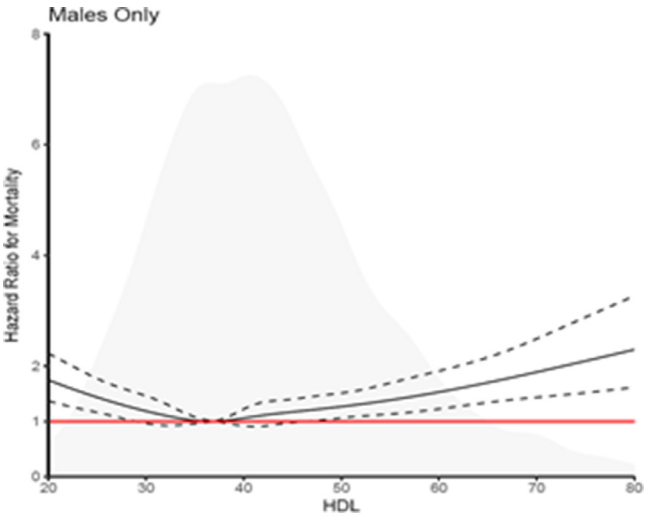

Figure 3. Male cohort, HDL on a continuous scale and risk of mortality. Solid Line represents risk-adjusted hazard ratio enclosed by 95% confidence intervals (dashed) from Cox regression using restricted cubic splines. The grey area in the background indicates distribution of HDL (mg/dl).

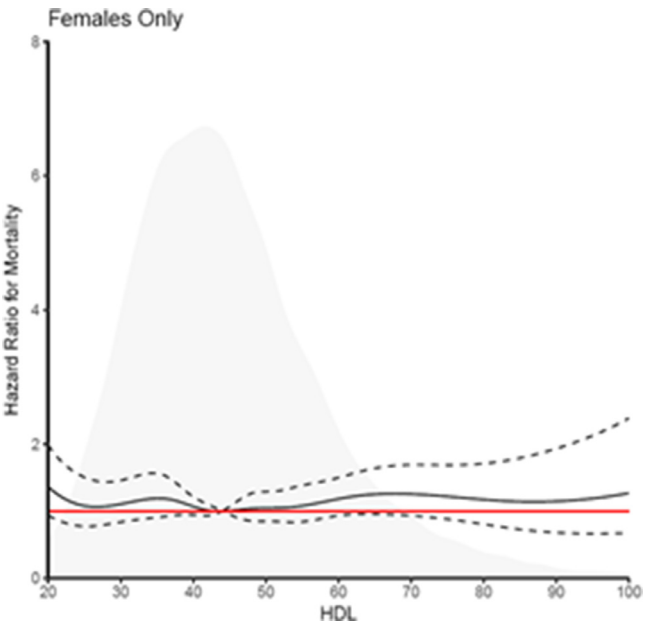

Figure 4. Female cohort, HDL on a continuous scale and risk of mortality. Solid black Line represents risk-adjusted hazard ratio enclosed by 95% confidence intervals (dashed) from Cox regression using restricted cubic splines. The grey area in the background indicates distribution of HDL (mg/dl).

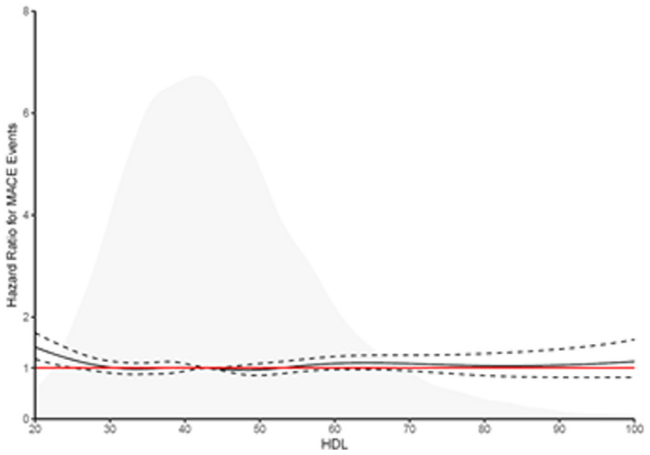

Figure 5A. MACCE - Overall cohort, HDL on a continuous scale and risk of first MACCE outcome. Solid Line represents risk-adjusted hazard ratio enclosed by 95% confidence intervals (dashed) from Cox regression using restricted cubic splines. The grey area in the background indicates distribution of HDL (mg/dl).

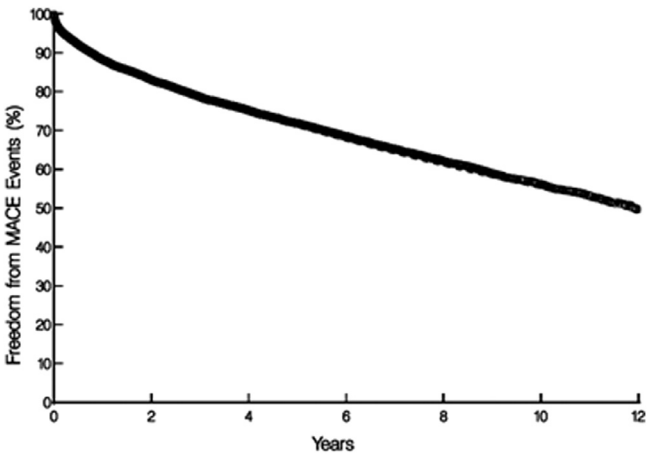

Figure 5B. Observed freedom from MACCE events – Overall cohort, Black Line represents parametric estimates of freedom from MACCE events for all patients. Dashed lines represent 68% Confidence Intervals. The dots represent nonparametric Kaplan-Meier estimates for freedom from MACCE events.

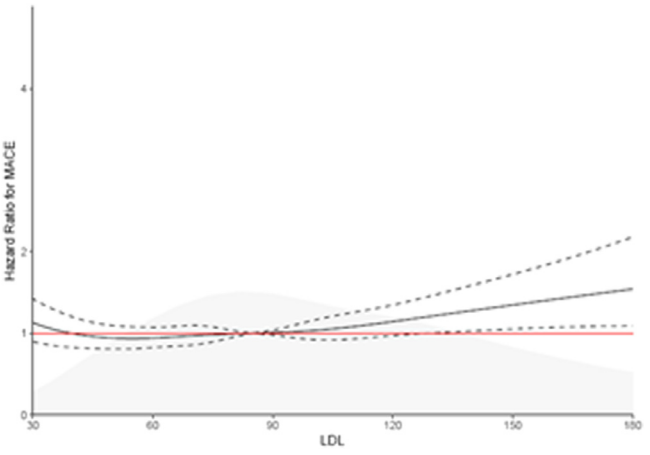

Figure 5C. MACCE - LDL- Overall cohort, LDL on a continuous scale and risk of first MACCE outcome. Solid Line represents risk-adjusted hazard ratio enclosed by 95% confidence intervals (dashed) from Cox regression using restricted cubic splines. The grey area in the background indicates distribution of LDL (mg/dl).

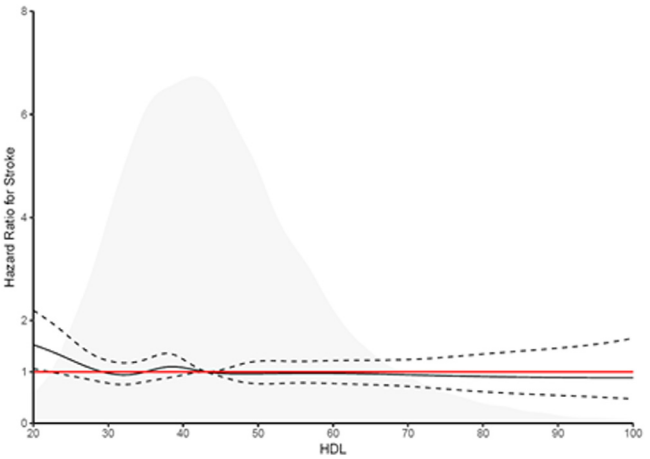

Figure 5D. Stroke - Overall cohort HDL on a continuous scale and risk of Stroke. Solid Line represents risk-adjusted hazard ratio enclosed by 95% confidence intervals (dashed) from Cox regression using restricted cubic splines. The grey area in the background indicates distribution of HDL.

with overall mortality in patients with cardiovascular disease.[14-16] Madsen et al. identified such a correlation between HDL-C levels and mortality in their analysis of patients from 2 prospective population-based studies (Copenhagen City Heart Study and the Copenhagen General Population Study). They found that an HDL-C level of 73mg/dl for men and 93mg/dl for women was associated with the lowest mortality risk, but that at higher levels (greater than 97 mg/dl in men and greater than 135 mg/dl in women), there was a paradoxical increase in all-cause mortality. However, their findings were limited by the small number of patients in their study with significantly elevated levels of HDL-C (n=2.5% of patients had HDL-C levels of >100mg/dl). Bowe et al. also observed a similar finding between HDL-C and overall mortality in patients with chronic kidney disease, although they noted that the presence of cardiovascular disease attenuated the results. In another study looking at patients without pre-existing cardiovascular conditions, Ko et al. again found a U-shaped association of HDL-C levels with mortality.[17]

Several hypotheses have been discussed in these recent studies regarding the association of elevated HDL-C levels in certain populations with increased risk of overall mortality and ASCVD events. In some patients, genetic mutations such as those affecting CETP, ABCA1, LIPC, and SCARB1 can result in high levels of serum HDL-C, but these do not appear to carry any mortality or ASCVD risk - benefit.[18,19] Drug trials that have targeted CTEP have also resulted in increased HDL-C levels, but again have not shown any reduction in mortality in patients with cardiovascular disease.[18,20,21,22] The Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health

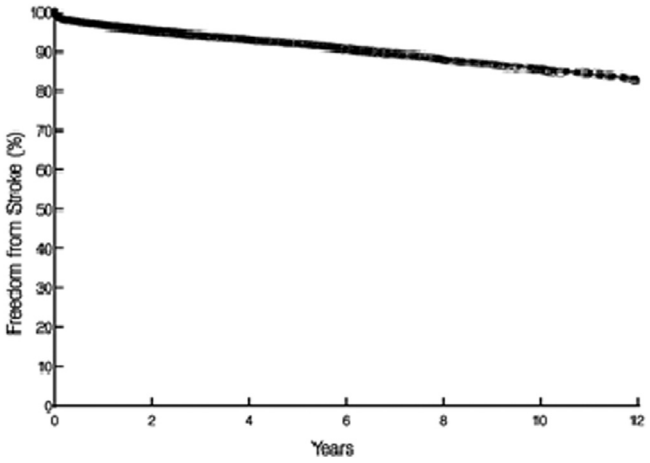

Figure 5E. Observed freedom from stroke – Overall cohort, Black Line represents parametric estimates of freedom from stroke for all patients. Dashed lines represent 68% confidence intervals. The dots represent nonparametric Kaplan-Meier estimates for freedom from Stroke.

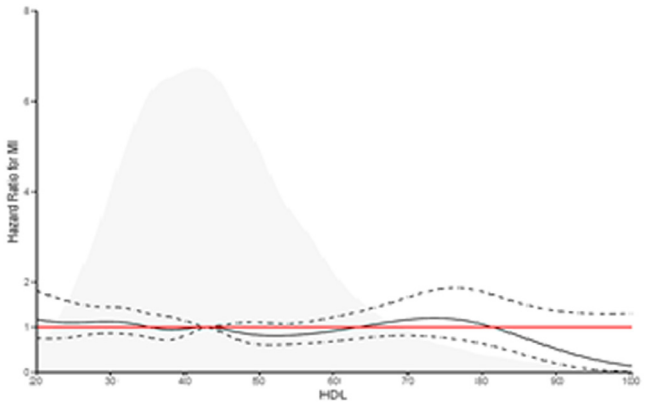

Figure 5F. Myocardial infarction - Overall cohort HDL on a continuous scale and risk of first MI. Solid Line represents risk-adjusted hazard ratio enclosed by 95% confidence intervals (dashed) from Cox regression using restricted cubic splines. The grey area in the background indicates distribution of HDL.

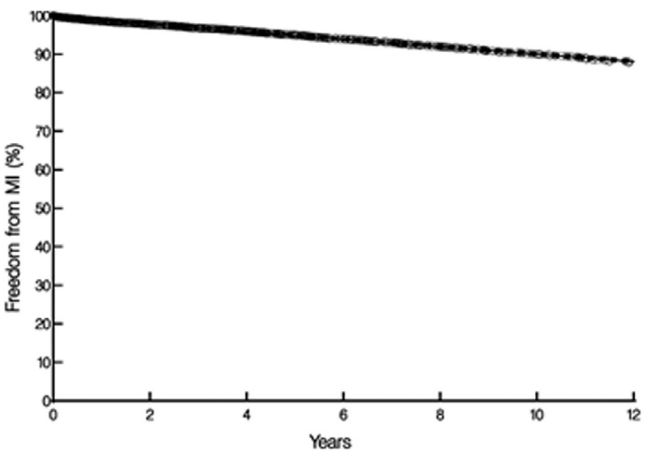

Figure 5G. Observed freedom from myocardial infarction – Overall cohort, Black Line represents parametric estimates of freedom from MI for all patients. Dashed lines represent 68% confidence intervals. The dots represent nonparametric Kaplan-Meier estimates for freedom from MI.

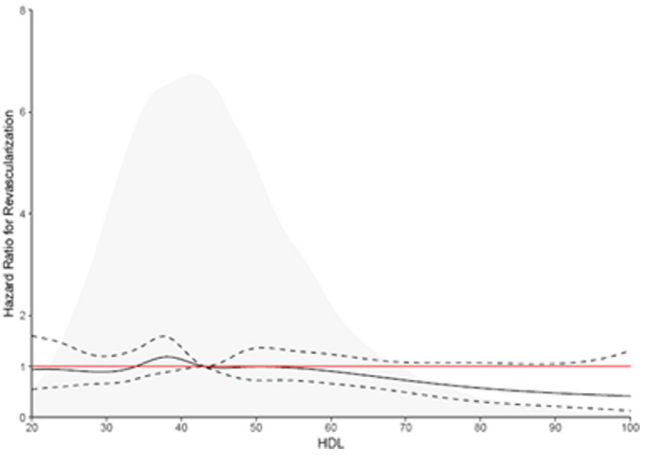

Figure 5H. Revascularization - Overall cohort, HDL on a continuous scale and risk of first revascularization. Solid Line represents risk-adjusted hazard ratio enclosed by 95% confidence intervals (dashed) from Cox regression using restricted cubic splines. The grey area in the background indicates distribution of HDL.

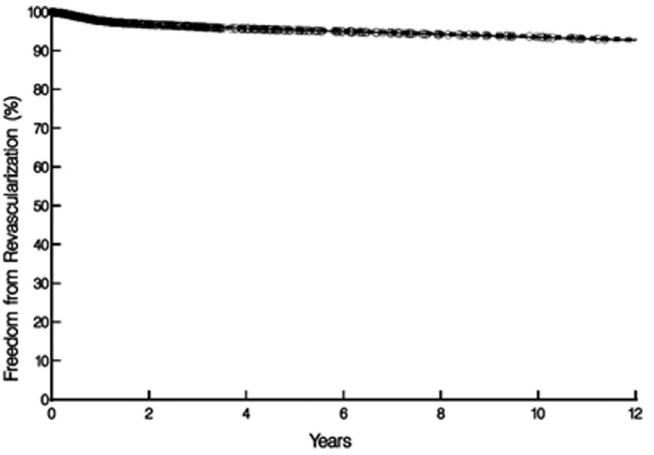

Figure 5I. Observed freedom from revascularization – Overall cohort, Black Line represents parametric estimates of freedom from revascularization for all patients. Dashed lines represent 68% confidence intervals. The dots represent nonparametric Kaplan-Meier estimates for freedom from Revascularization.

Outcomes (AIM-HIGH) and Heart Protection Study 2 –Treatment of HDL to Reduce the Incidence of Vascular Event (HPS2-THRIVE) studies, which used the extended dose of niacin in patient who were previously taking statins to increase HDL-C levels, did not demonstrate incrementally lower MACE.[23,24]

One possible explanation for loss of protective benefit with elevated HDL-C levels is related to structural changes in the protein associated with the HDL particle itself. It has been noted that very large HDL particles in patients with high HDL-C levels are overloaded with cholesterol, resulting in a dysfunctional HDL. The efflux potential of cholesterol from extrahepatic cells may be negatively impacted, effectively reducing the selective uptake of cholesterol mediated by scavenger receptor SR-B1. This can lead to a lack of clinical benefit despite increasing HDL-C levels, as these very large HDL particles lose their anti-atherogenic

and antioxidative functions.[13,25] This phenomenon was previously seen in 2 large prospective studies, the IDEAL (Incremental Decrease in End Points through Aggressive Lipid Lowering) trial and the EPIC (European Prospective Investigation into Cancer and Nutrition)-Norfolk case-control study, where very high plasma HDL-C levels (>70mg/dl) and very large HDL particle size (>9.53nm) was linked with an increased risk of cardiovascular disease.[26,13] Furthermore, in certain conditions, including diabetes, visceral obesity, CAD, acute and chronic inflammatory conditions, HDLs can directly act in a dysfunctional and pro-inflammatory role, paradoxically increasing ASCVD risk.[27,28] In addition, our results showed significant increased mortality in men but not women at high and low HDL-C levels. It could be due to the different hormonal status in both the genders.[34] Furthermore, we have reported that increases in LDL-C levels are also associated with increased risk of overall mortality and MACCE events. In the CAD population with increased levels of LDL-C, there is a predominance of "small dense" LDL particles rather than "large fluffy" LDL particles. Small dense LDL particles are associated with an increased atherogenesis due to a longer circulating time in plasma, enhanced arterial proteoglycan binding, and increased oxidation and permeability through the endothelial barrier.[29-31] This study supports that LDL-C levels should be aggressively reduced with statins to decrease the MACCE events in CAD patients.

Overall, the mechanisms underlying the association between highly elevated HDL-C and increased overall mortality remain unclear. In this study, we highlight a concerning finding with very high HDL-C levels in a population with known CAD. Clinicians should be aware of the fact that elevated HDL−C levels may not be protective against cardiovascular diseases, and therefore attempts to increase HDL-C levels do not appear to confer any benefit to overall mortality or protection against cardiovascular diseases. Due to the predominance of small dense LDL particles in this population, clinicians should focus on aggressively using statins to reduce the levels of small dense LDL particles to lower ASCVD risk.[32]

The primary strength of this study is the large patient population reviewed, all of whom had undergone PCI, had detailed information regarding their cholesterol levels within 1 year of their procedure and were properly adjusted for regarding covariables including other aspects of their lipid profiles. The population studied included all ethnicities and may be more reflective of a general population. We used the same model with spline curves to assess the association of LDL-C levels with mortality and MACCE rate. Several limitations should be noted in the context of the present findings. The observational nature of the study precludes the ability to determine the causal relationship between HDL-C levels and overall mortality; only an association has been determined. Unmeasured confounders or reverse causation remain possible etiologies of the observed association. Our findings may not be generalizable in the general population. We also do not have information regarding possible confounders such as cause of death and external injury including poisoning and road traffic accident responsible for patient deaths. The follow-up of patients after-PCI was performed passively via the electronic medical record. Any patients who reached an end point outside the country would not have been captured or reported in the study. Furthermore, co-variants such as alcohol intake and smoking status were not included due to lack of sufficient details available in the electronic medical record.

In conclusion, we observed a U-shaped association between HDL-C concentrations and overall mortality in patients who underwent PCI. Elevated HDL-C levels were not associated with lower MACCE.

Disclosures

The authors declare no conflict of interests

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.01.014.

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