High-density lipoprotein cholesterol does not predict future cardiovascular events in patients treated with statins for secondary prevention: an observation from the REAL-CAD study

Authors:
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On behalf: The REAL-CAD study

Topic(s):
Secondary Prevention

Background:
The relation between high-density lipoprotein cholesterol (HDL-C) level after statin therapy and cardiovascular events in patients with stable coronary artery disease remains unclear.

Purpose:
We sought to determine the association of the HDL-C level after statin therapy with cardiovascular events in stable coronary artery disease patients.

Methods:
This study was a post-hoc analysis of the Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease (REAL-CAD) study, which is randomised, open-label, blinded endpoint, physician-initiated, superiority clinical trial. Enrollment was from January 2010 to March 2013, and follow-up was through January 2016. From the main study, we excluded the patients without either HDL-C data at baseline or 6 months, with occurrence of the primary outcome at 6 months and reported poor adherence for pitavastatin. The primary outcome of interest was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal ischemic stroke, or unstable angina requiring emergent admission after 6 months from randomisation, consistent with the primary analysis of the trial. We constructed landmark Cox proportional hazards regression models with the 18 selected clinically relevant risk-adjusting variables during the entire follow-up period starting at 6 months after randomisation. Absolute and relative changes of HDL-C level were defined as (6 months value – baseline value) and (absolute change / baseline value) × 100, respectively.

Results:
Among 14,774 participants in the REAL-CAD study, 9,221 patients were included in this analysis (7652 [83.0%] male; median [IQR] age, 70 [63-75] years; median [IQR] HDL-C, 49 [42-57] mg/dL; median [IQR] low-density lipoprotein cholesterol [LDL-C], 88 [75-101] mg/dL). During a median follow-up period of 4.0 (IQR 3.2-4.7) years, the primary outcome occurred in 417 (4.5%) patients. There was no significant difference in crude and adjusted cumulative incidence of the primary outcome among the quartiles of HDL-C level at 6 months (Figure 1). The adjusted risks of all the HDL-C related variables (baseline value, 6 months value, absolute and relative changes) for the primary outcome were not significant (Figure 2). Furthermore, the adjusted hazard ratio (HR) as HDL-C level at 6 months increased by 10 mg/dL remained non-significant for the primary outcome for each on-treatment LDL-C level at 6 months (<70 mg/dL [HR 0.97, 95%CI 0.82-1.15], 70-100 mg/dL [HR 1.10, 95%CI 0.98-1.24], and ≥100 mg/dL [HR 0.94, 95%CI 0.78-1.13]). There was also no significant association between HDL-C level at 6 months and the primary outcome both in the low (1 mg/day [HR 1.02, 95%CI 0.91-1.14], increased by 10 mg/dL) dose and high (4 mg/day [HR 1.04, 95%CI 0.91-1.19]) dose pitavastatin groups.

Conclusion:
After statin therapy with modestly controlled LDL-C, HDL-C level has little prognostic value in patients with stable coronary artery disease.
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Figure 1. Landmark analysis

Primary Outcome (Crude)

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Primary Outcome (Adjusted)

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Figure 2. Adjusted risks of HDL-C values for primary outcome

At baseline

Adjusted hazard ratio

HDL-C (mg/dL)

At 6 months

Adjusted hazard ratio

HDL-C (mg/dL)

Absolute change

Adjusted hazard ratio

HDL-C (mg/dL)

Relative change

Adjusted hazard ratio

Change of HDL-C (%)

Red line; hazard ratio with penalised smoothing splines adjusted by covariates. Dashed yellow line; its 95% confidence interval.

Dotted line; high dose pitavastatin group (4 mg/day). Solid line; low dose pitavastatin group (1 mg/day).