Supplementary Online Content

Sabatine MS, Wiviott SD, Im KA, Murphy SA, Giugliano RP. Efficacy and safety of further lowering of low-density lipoprotein cholesterol in patients starting with very low levels: a meta-analysis. JAMA Cardiol. Published online August 1, 2018. doi:10.1001/jamacardio.2018.2258.

eMethods.

eResults.

eFigure. Literature Search

This supplementary material has been provided by the authors to give readers additional information about their work.
eMethods

Potential trials were identified from MEDLINE. The following search terms were used: *Cholesterol, LDL* and [Anticholesteremic Agents or Hypolipidemic Agents] and *Cardiovascular Diseases*. The MEDLINE search was limited to randomized controlled trials, human, and published between 2015 and April 2018. Results were supplemented from the reference files of all authors and from reference lists of original articles, reviews, and meta-analyses. To qualify trials had to be a double-blind, controlled, dedicated cardiovascular outcomes trial of an LDL-C lowering drug, had to use a reliable method of LDL-C measurement (ie, preparative ultracentrifugation if a CETP inhibitor was used), have a median follow-up for at least 2 years, and present data on patients starting with a mean or median LDL-C \( \leq 1.8 \) mmol/L (70 mg/dL), as that is a treatment threshold recommended in multiple guidelines.\(^1\)\(^2\)\(^3\)

Lipid data, cardiovascular outcome data and safety data for each relevant trial were extracted using a structured form and reviewed by \( \geq 2 \) authors. Whenever possible, we used the difference in LDL-C between treatment arms in a trial that was calculated using imputation for missing values as per the CTTC method. Muscle-related events (typically myalgias and/or myositis) and elevation in aminotransferases (typically \( \geq 3 \) times the upper limit of normal of ALT or AST) were based on the definition in each trial. If not available, numbers of events estimated from published proportions and number of subjects in each arm.

For the meta-regression for achieved LDL-C and rate of cardiovascular outcomes, data on the number of events and person years of followup (estimated from the number of patients in the arm of the trial and the median follow-up in the trial) were used to generate event rates and 95% confidence intervals, and a linear regression model of the natural log of the incidence rates was used to generate the slope of the regression line and intercept. Given the differential follow-up in the trials, rates were extrapolated to 5 years for graphical display.
eResults

HOPE-3 studied rosuvastatin in intermediate-risk individuals. It was excluded because the lowest reported starting LDL-C subgroup was only ≤2.9 mmol/L (112 mg/dL). However, it should be noted that in that subgroup, the mean starting LDL-C was 2.3 mmol/L, the LDL-C difference between statin and control arms was 0.5 mmol/L (data from rosuvastatin/candesartan vs. double-placebo comparison), and the hazard ratio for the effect of statin therapy on major vascular events was 0.70 (95% CI 0.52-0.96). The hazard ratio per 1 mmol/L (38.7 mg/dL) reduction in LDL-C was therefore 0.50 (95% CI 0.28-0.92). If these data were added to our meta-analysis the overall summary effect would change from 0.79 (0.71-0.87) to 0.78 (95% CI 0.70-0.85).

ACCELERATE studied the CETP inhibitor evacetrapib in high-risk patients. It was excluded because LDL-C was not measured by beta-quantification and it has been shown that in patients on CETP inhibitors both the Friedewald estimation and direct LDL-C assays underestimate LDL-C and therefore would overestimate LDL-C reduction with CETP inhibition. In the subgroup of patients with an LDL-C <1.8 mmol/L, the hazard ratio for the effect of evacetrapib on major vascular events was 0.99 (with estimated 95% CI of 0.85-1.18). The LDL-C levels were not provided in this subgroup. Overall, evacetrapib reduced LDL-C from baseline by 31% (whereas it rose by 6% in the placebo arm). If one assumes the median starting LDL-C was 1.8 mmol/L in this subgroup (likely an overestimate), then the absolute difference in LDL-C between the arms would be approximately 0.67 mmol/L. The hazard ratio per 1 mmol/L reduction in LDL-C would therefore be approximately 0.99 (95% CI 0.78-1.27). If these data were added to our meta-analysis the overall summary effect would change from 0.79 (0.71-0.87) to 0.81 (95% CI 0.74-0.89). However, based on data from another CETP inhibitor trial, REVEAL, which had LDL-C levels calculated both by direct assays and preparative ultracentrifugation), the LDL-C reduction by preparative ultracentrifugation was only 41% of what it was by direct assay. Based on those data, one might reasonably estimate that evacetrapib reduced LDL-C by 12.7% (41% of 31%), in which case the absolute difference in LDL-C between the arms would be approximately 0.3 mmol/L (13 mg/dL). The hazard ratio per 1 mmol/L reduction in LDL-C would therefore be approximately 0.97 (95% CI 0.61-1.62). If these data were added to our meta-analysis the overall summary effect would change from 0.79 (0.71-0.87) to 0.79 (95% CI 0.72-0.87).
ODYSEY studied the PCSK9 inhibitor alirocumab in patients with an acute coronary syndrome in the past year. It was excluded because the lowest reported starting LDL-C subgroup was only <2.1 mmol/L (80 mg/dL). However, it should be noted that in that subgroup, the hazard ratio for the effect of alirocumab on major vascular events was 0.86 (95% CI 0.74-1.01). The difference in LDL-C between the experimental and control arms was not provided. However, overall in the trial, at the midpoint of follow-up alirocumab lowered LDL-C by approximately 46% (the dose of alirocumab was down-titrated if LDL-C was <0.6 mmol/L). If one assumes the starting LDL-C was 2.1 mmol/L (likely an overestimate), then the absolute difference in LDL-C between the arms would be approximately 0.95 mmol/L (likely an overestimate of the LDL-C difference because the protocol-mandated down-titration of alirocumab in patients achieving very low LDL-C levels would be much more likely to occur in this subgroup). The hazard ratio per 1 mmol/L reduction in LDL-C would therefore be approximately 0.85 (95% CI 0.73-1.01). If these data were added to our meta-analysis the overall summary effect would change from 0.79 (0.71-0.87) to 0.80 (95% CI 0.74-0.87).

eFigure. Literature Search.

28 Records identified through database searching  
(publication dates: January 2015-April 2018)  
4 Additional records identified through other sources

32 Records screened

29 Records excluded
13 Not a cardiovascular outcomes trial  
7 Non-relevant secondary analyses  
4 Design or review paper  
5 Ineligible  
    HOPE-3: lowest starting LDL-C subgroup was only ≤2.9 mmol/L  
    ACCELERATE: lacked accurate measurement of LDL-C in arm treated with CETPi  
    FOURIER: lowest starting LDL-C subgroup was only <2.1 mmol/L (but additional record included that had data on patients with starting LDL-C <1.8 mmol/L)  
    SPIRE I & II: follow-up <2 years  
    ODYSSEY Outcomes: lack of data on patients with LDL-C ≤1.8 mmol/L

3 Articles included