JAMA | Original Investigation

Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions
A Systematic Review and Meta-analysis

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IMPORTANCE The comparative clinical benefit of nonstatin therapies that reduce low-density lipoprotein cholesterol (LDL-C) remains uncertain.

OBJECTIVE To evaluate the association between lowering LDL-C and relative cardiovascular risk reduction across different statin and nonstatin therapies.

DATA SOURCES AND STUDY SELECTION The MEDLINE and EMBASE databases were searched (1966-July 2016). The key inclusion criteria were that the study was a randomized clinical trial and the reported clinical outcomes included myocardial infarction (MI). Studies were excluded if the duration was less than 6 months or had fewer than 50 clinical events. Studies of 9 different types of LDL-C reduction approaches were included.

DATA EXTRACTION AND SYNTHESIS Two authors independently extracted and entered data into standardized data sheets and data were analyzed using meta-regression.

MAIN OUTCOMES AND MEASURES The relative risk (RR) of major vascular events (a composite of cardiovascular death, acute MI or other acute coronary syndrome, coronary revascularization, or stroke) associated with the absolute reduction in LDL-C level; 5-year rate of major coronary events (coronary death or MI) associated with achieved LDL-C level.

RESULTS A total of 312 175 participants (mean age, 62 years; 24% women; mean baseline LDL-C level of 3.16 mmol/L [122.3 mg/dL]) from 49 trials with 39 645 major vascular events were included. The RR for major vascular events per 1-mmol/L (38.7-mg/dL) reduction in LDL-C level was 0.77 (95% CI, 0.71-0.84; P < .001) for statins and 0.75 (95% CI, 0.66-0.86; P = .002) for established nonstatin interventions that work primarily via upregulation of LDL receptor expression (ie, diet, bile acid sequestrants, ileal bypass, and ezetimibe) (between-group difference, P = .72). For these 5 therapies combined, the RR was 0.77 (95% CI, 0.75-0.79, P < .001) for major vascular events per 1-mmol/L reduction in LDL-C level. For other interventions, the observed RRs vs the expected RRs based on the degree of LDL-C reduction in the trials were 0.94 (95% CI, 0.89-0.99) vs 0.91 (95% CI, 0.90-0.92) for niacin (P = .24); 0.88 (95% CI, 0.83-0.92) vs 0.94 (95% CI, 0.93-0.94) for fibrates (P = .02), which was lower than expected (ie, greater risk reduction); 1.01 (95% CI, 0.94-1.09) vs 0.90 (95% CI, 0.89-0.91) for cholesteryl ester transfer protein inhibitors (P = .002), which was higher than expected (ie, less risk reduction); and 0.49 (95% CI, 0.34-0.71) vs 0.61 (95% CI, 0.58-0.65) for proprotein convertase subtilisin/kexin type 9 inhibitors (P = .25). The achieved absolute LDL-C level was significantly associated with the absolute rate of major coronary events (11 301 events, including coronary death or MI) for primary prevention trials (1.5% lower event rate [95% CI, 0.5%-2.6%] per each 1-mmol/L lower LDL-C level; P = .008) and secondary prevention trials (4.6% lower event rate [95% CI, 2.9%-6.4%] per each 1-mmol/L lower LDL-C level; P < .001).

CONCLUSIONS AND RELEVANCE In this meta-regression analysis, the use of statin and nonstatin therapies that act via upregulation of LDL receptor expression to reduce LDL-C were associated with similar RRs of major vascular events per change in LDL-C. Lower achieved LDL-C levels were associated with lower rates of major coronary events.

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ow-density lipoprotein cholesterol (LDL-C) is a well-established risk factor for cardiovascular disease, as evidenced by epidemiological and Mendelian randomization studies. Recognizing the importance of LDL-C, the National Heart, Lung, and Blood Institute formed the National Cholesterol Education Program more than 30 years ago to educate both the medical community and the general public about the need to lower levels of blood cholesterol to reduce the risk of major vascular events.[1]

Although there is consensus about the value of lowering LDL-C, recommendations about how to do so have shifted over time.[2-5] The clinical benefit of lowering LDL-C with statins remains widely accepted, as does the concept demonstrated by the Cholesterol Treatment Trialists' Collaboration that the magnitude of clinical benefit observed with statins is proportional to the absolute reduction in LDL-C.[6] In contrast, the clinical benefit of the previously recommended use of nonstatin therapies to lower LDL-C is less definitive.[7]

The 2013 American College of Cardiology/American Heart Association guideline on the treatment of blood cholesterol emphasized the use of statins to lower LDL-C,[3] whereas a more recent American College of Cardiology expert consensus document recommended considering adding certain nonstatin therapies to lower LDL-C, such as bile acid sequestrants, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.[5] The use of niacin, fibrates, or both is not recommended, which parallels the recent withdrawal by the US Food and Drug Administration of approval for niacin and fibrates in combination with a statin.[8] The purpose of this meta-regression analysis was to evaluate the association between lowering LDL-C and cardiovascular risk reduction across different therapies to lower LDL-C.

Methods

A systematic review and trial-level meta-regression analysis of randomized clinical trials that evaluated the effect of therapy to lower LDL-C on cardiovascular outcomes was performed and the results are reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.[9] Potential trials were identified from (1) MEDLINE and EMBASE using the search terms *LDL lowering* and *clinical outcomes*, limited to *randomized controlled trials* and *human* and published between 1966 and July 2016 (eMethods in the Supplement); (2) the reference files of M.G.S. and M.S.S.; (3) reference lists of original articles, reviews, and meta-analyses; (4) a review of abstracts of major cardiovascular meetings held during the past 2 years; and (5) by contacting experts.

The following inclusion criteria were required to be eligible for the meta-regression analysis: (1) randomized clinical trial; (2) single intervention difference between the experimental and control group (which could either be therapy to lower LDL-C vs no therapy or, for 6 trials, more intensive vs less intensive statin therapy); and (3) reported clinical cardiovascular outcomes that at least included myocardial infarction (MI). Trials were excluded for the following reasons: (1) duration of less than 6 months (a timeframe during which

Key Points

Question What is the association between lowering low-density lipoprotein cholesterol (LDL-C) and cardiovascular risk reduction across different therapeutic interventions?

Findings In a meta-regression analysis of 49 clinical trials with 312 175 participants, each 1-mmol/L (38.7-mg/dL) reduction in LDL-C level was associated with a relative risk (RR) of major vascular events of 0.77 (95% CI, 0.71-0.84; $P < .001$) for statins and 0.75 (95% CI, 0.66-0.86; $P = .002$) for established nonstatin interventions that act primarily via upregulation of LDL receptor expression.

Meaning These data suggest statins and nonstatin therapies that act through upregulation of LDL receptor expression are associated with similar cardiovascular risk reduction per decrease in LDL-C. The clinical value of adding specific nonstatin interventions to lower LDL-C to background statin therapy should be confirmed in appropriately powered clinical trials.

a clinical benefit of lipid-lowering therapy would not be expected to emerge[10]); (2) fewer than 50 clinical events during the course of the trial (to exclude small trials with unreliable hazard ratios); (3) study population focused on participants with significant competing risks (ie, heart failure or chronic kidney disease because lipid-lowering therapy has been shown to be less clinically effective due to competing nonatherosclerotic risks[6]); or (4) experimental intervention with known off-target adverse effects on cardiovascular outcomes (which would impair the ability to judge the benefit of the LDL-C reduction).

The following information was obtained from each trial using a structured form independently by 2 of the authors (M.G.S. and M.S.S.): sample size, whether the trial studied a primary or secondary prevention population, intervention and comparison therapy, trial duration, reduction in LDL-C levels and non–high-density lipoprotein cholesterol (non-HDL-C) levels in each group, achieved LDL-C levels in each treatment group and the difference between groups, absolute major vascular and coronary event rates in both treatment groups, and hazard ratios (or risk ratios in trials that did not report hazard ratios) with 95% CIs for the treatment effect. In the earlier trials that did not report LDL-C levels, LDL-C values at baseline and while in the study were estimated from total cholesterol levels (the Supplement provides additional details).

Outcomes from each trial were selected to most closely approximate the target composite end point of major vascular events, which consisted of cardiovascular death, acute MI or other acute coronary syndrome, coronary revascularization, and stroke when available because all these events have been shown to be reduced by therapies to lower LDL-C. In some instances, the selected outcome that best matched the target composite was a secondary composite end point for the original trial. The specific outcome selected for each trial is listed in eTables 1-9 in the Supplement. All disagreements were discussed and resolved by consensus.

The interventions were divided into 4 groups: (1) statins; (2) nonstatin therapies that ultimately lower LDL-C predomi-

nantly by lowering intrahepatic cholesterol, thereby leading to upregulation of LDL receptor expression, and have been studied in dedicated cardiovascular outcomes trials (ie, diet, bile acid sequestrants, ileal bypass surgery, and ezetimibe)[11-14]; (3) interventions that do not reduce LDL-C levels primarily through upregulation of LDL receptor expression (ie, fibrates, niacin, cholesteryl ester transfer protein [CETP] inhibitors)[15-17]; and (4) PCSK9 inhibitors, which upregulate LDL-C clearance through the LDL receptor,[18] but for which dedicated cardiovascular outcome trials have not yet been completed (and therefore were considered separately to evaluate how the data to date compare with established therapies that upregulate LDL receptor expression).

The association between the absolute amount of LDL-C reduction of an intervention (calculated as the difference in achieved LDL-C levels between the 2 treatment groups) and the hazard or risk ratio for major vascular events with that intervention was evaluated. The hazard ratios were subsequently treated as risk ratios when the results of studies were pooled and then the term *risk ratio* was used to describe the effect estimate. Meta-regression analyses were performed using random-effects models with the restricted maximum likelihood estimation estimator for between-study variability and the Knapp and Hartung adjustment for estimation of standard errors of the estimated coefficients to calculate summary effect estimates (which are presented as relative risk (RR) with 95% CIs, P values, and R^2 values (a measure of the proportion of between-study variability accounted for by the variable).[19,20] For statin trials, an additional meta-regression analysis was performed to evaluate the association between the percentage (rather than the absolute) of LDL-C reduction for an intervention and the RR for major vascular events with the intervention. Two-sample z testing was performed to compare the effect sizes per each 1-mmol/L (38.7-mg/dL) reduction in LDL-C level between the different treatment types.

A random-effects meta-regression with the intercept set at 0 was used to estimate the RR per each 1-mmol/L reduction in LDL-C level for the combination of statins and nonstatin therapies that act predominantly via upregulation of LDL receptor expression and have been studied in dedicated cardiovascular outcomes trials. The mean weighted LDL-C reduction, RR, and 95% CI were then estimated for each of the 9 treatment types separately using fixed-effects meta-analysis with weighting by inverse variance and plotted relative to the meta-regression line. Two-sample z testing was performed to compare the observed RR for each of the 9 interventions with the regression line to evaluate for possible differences in estimated effect size per unit reduction in LDL-C by treatment type. Analogous analyses were performed using non-HDL-C instead of LDL-C.

The association between the achieved LDL-C level and the estimated 5-year rate of major coronary events (coronary death or MI) was evaluated using random-effects meta-regression analysis of the data from each group (experimental and control) in more recent trials of statins and established nonstatin therapies that ultimately act predominantly via upregulation of LDL receptor expression and that had the necessary infor-

mation available (eMethods in the Supplement). For this analysis, trials were divided into primary prevention vs secondary or mixed prevention (excluding studies of patients with acute coronary syndromes given the nonlinear accrual of events) participant populations.

Assessments of the study quality, consistency of results, and publication bias appear in the Supplement. Additional sensitivity analyses appear in the eMethods.

Statistical significance was assessed at a nominal α level of .05. All reported P values are 2-sided. Statistical analyses were performed using the Metafor package version 3.30 (R Project for Statistical Computing)[20] and the Comprehensive Meta Analyses version 3.3.070 (Biostat Inc).
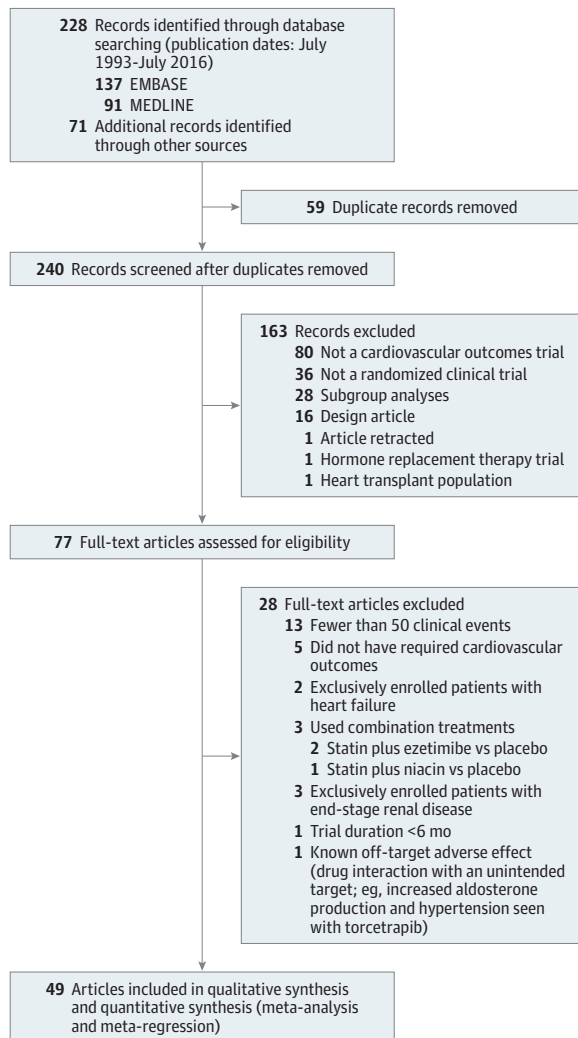
Results

A total of 240 citations were identified and reviewed for eligibility (**Figure 1**) and 49 trials, spanning 9 different treatment modalities were included in the meta-regression analysis (**Table**[21-25] and eTables 1-9 in the Supplement). There were 25 statin trials. There were 8 trials of established nonstatin therapies that ultimately act predominantly via upregulation of LDL receptor expression (4 diet trials, 2 trials of bile acid sequestrants, 1 trial of ileal bypass surgery, and 1 trial of ezetimibe). There were 15 trials of interventions that do not reduce LDL-C levels primarily through upregulation of LDL receptor expression (9 trials with fibrates, 3 trials with niacin [1 of which was a multigroup trial that also studied fibrates], and 3 trials with CETP inhibitors). There were 2 trials with PCSK9 inhibitors. These trials included a total of 312 175 participants with 39 645 major vascular events. The mean follow-up was 4.3 years, resulting in approximately 1.3 million person-years of follow-up.

For the 25 statin trials, each 1-mmol/L (38.7-mg/dL) reduction in LDL-C level was associated with an RR of 0.77 (95% CI, 0.71-0.84; P < .001) for major vascular events (**Figure 2**A).[26-48] The results were similar in patient populations in the primary prevention trials (RR per 1-mmol/L reduction in LDL-C, 0.70 [95% CI, 0.53-0.93]) and in the secondary prevention trials (RR per 1-mmol/L reduction in LDL-C, 0.79 [95% CI, 0.73-0.86]) (eFigures 1 and 2 in the Supplement). The absolute reduction in LDL-C accounted for 98% of the between-study variability (R^2 value) in the reduction of major vascular events, whereas the percentage reduction in LDL-C only accounted for 79%.

A similar association between absolute lowering of LDL-C and the RR for major vascular events was seen in the 8 trials of established nonstatin therapies that ultimately act predominantly via upregulation of LDL receptor expression. Specifically, each 1-mmol/L reduction in LDL-C was associated with an RR of 0.75 (95% CI, 0.66-0.86; P = .002) in major vascular events (P = .72 for between-group difference with statin therapy) (Figure 2B).[49-54]

Combining the data from all 33 of the aforementioned trials generated the meta-regression line (predicted RR of major vascular events for various levels of LDL-C reduction) in **Figure 3**, in which each 1-mmol/L reduction in LDL-C was associated with an RR of 0.77 (95% CI, 0.75-0.79) in major vascular events.

Figure 1. Identification and Selection of Randomized Clinical Trials Evaluating the Effect of Low-Density Lipoprotein Cholesterol Lowering Therapy on Cardiovascular Outcomes

There were 49 articles that reported the results from 49 trials with 50 comparisons (the Coronary Drug Project[21] was a multigroup trial that compared both fibrates and niacin individually with placebo).

A summary of each intervention is plotted on the graph based on the weighted between-group difference in LDL-C in the trials and the weighted RR of major vascular events calculated from the meta-analyses (eFigures 3-12 in the Supplement). The observed RR of major vascular events for each of the 5 different established interventions that ultimately act predominantly through upregulation of LDL receptor expression (ie, statins, diet, bile acid sequestrants, ileal bypass, and ezetimibe) was within 0.02 (ie, 2%) of the predicted value from the regression line, suggesting consistent clinical benefit normalized to the magnitude of LDL-C reduction, regardless of the treatment class.

In terms of the other interventions, the observed RR of 0.94 (95% CI, 0.89-0.99) for major vascular events for niacin was greater (ie, less risk reduction) than the expected RR

from meta-regression of 0.91 (95% CI, 0.90-0.92; P = .24), but with 95% CIs that encompass the regression line and z score testing showing no significant difference (P = .24). The observed RR of 0.88 (95% CI, 0.83-0.92) for fibrates was lower (ie, greater risk reduction) than the expected RR of 0.94 (95% CI, 0.93-0.94) (P = .02). Fibrates also substantially reduce levels of very low-density lipoprotein, an atherogenic particle that contains both cholesterol and triglycerides. When recalculating the regression slope using non-HDL-C, the RR per 1-mmol/L reduction in non-HDL-C was 0.80 (95% CI, 0.77-0.82), which was similar to the RR with LDL-C reduction. The observed RR associated with fibrates was shifted to the right and was no longer statistically significantly different than the expected RR from the regression line for non-HDL-C (eFigure 13 in the Supplement). There was a significant association between the degree of lowering for triglycerides and the RR of major vascular events with fibrates (eFigure 14 in the Supplement).

The observed RR of 1.01 (95% CI, 0.94-1.09) associated with CETP inhibitors was significantly greater than the expected RR of 0.90 (95% CI, 0.89-0.91; P = .002) (ie, less risk reduction) with no appreciable clinical benefit in a meta-analysis of the compounds studied to date. In a sensitivity analysis in which the LDL-C reductions were adjusted for potential inaccuracies stemming from use of the Friedewald equation,[55] the effect estimate still differed from the meta-regression line (P = .01). The estimated RR of 0.49 (95% CI, 0.34-0.71) associated with PCSK9 inhibitors was numerically lower, but not significantly different, than the expected RR of 0.61 (95% CI, 0.58-0.65), with wide 95% CIs that included the regression line (P = .25).

There was a significant association between the observed absolute achieved LDL-C and the 5-year rates of major coronary events (coronary death or MI, n = 11 301) in the intervention and control groups among the trials of statins and established nonstatin therapies that ultimately act predominantly via upregulation of LDL receptor expression (eTable 10 in the Supplement). This association was seen in primary prevention trials (1.5% lower event rate [95% CI, 0.5%-2.6%] per 1-mmol/L lower LDL-C; P = .008) and secondary prevention trials (4.6% lower event rate [95% CI, 2.9%-6.4%] per 1-mmol/L lower LDL-C; P < .001) (Figure 4). Baseline LDL-C was not a significant variable in either of these models.

A review of study quality and analyses for heterogeneity of results and publication bias are provided in eTable 11 through eTable 20 in the Supplement. No significant heterogeneity was seen. There was no evidence for substantively important publication bias. A series of sensitivity analyses are reported in the eResults in the Supplement and showed no substantive differences.

Discussion

In this systematic review and meta-regression analysis of 49 trials involving 9 different interventions to lower LDL-C that included more than 300 000 patients and approximately 40 000 major vascular events, there was a similar association

Table. Trials Included in the Meta-analysis

		Type of Nonstatin Therapy								
	Statin	Diet	Bile Acid Sequestrants	Ileal Bypass	Ezetimibe	Fibrates	Niacin	CETP Inhibitors	PCSK9 Inhibitors	Total
No. of trials	25	4	2	1	1	9	3	3	2	49[a]
No. of participants	177 088	1903	6084	838	18 144	41 520	32 995	29 586	6806	312 175[a]
Age, y[b]	63	62	50	51	64	56	65	62	59	62
Female sex, No. (%)	49 480 (29)[c]	0	1184 (19)	78 (9)	4416 (24)	5729 (14)	4948 (15)	6227 (21)	3094 (45)	75 156 (24)
Baseline LDL-C, mmol/L[d]	Range, 2.5-5.0	Range, 4.0-5.6	Range, 5.3-6.1	Mean (SD), 4.6 (0.96)	Mean (SD), 2.4 (0.52)	Range, (2.6-4.9)	Range, 1.6-4.4	Range, 2.0-2.1	Range, 3.1-3.2	Range, 1.6-6.1
No. of major vascular events	20 962	489	470	207	5314	4894	5136	2901	111	39 645[a]
Duration of follow-up, mean, y[e]	4.5	4.4	5.4	9.7	6.0	5.1	3.9	2.3	1.2	4.3

Abbreviations: CETP, cholesteryl ester transfer protein; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

To convert LDL-C from mmol/L to mg/dL, divide by 0.0259.

[a] The Coronary Drug Project[21] was a multigroup trial that studied both fibrates and niacin individually compared with placebo. The participants and events in the placebo group were only counted once for the total column.

[b] Indicates the mean or median age (depending on what was presented in each trial) of participants in the individual trials. Average age was not available for the following trials: for statins, GISSI-Prevention[22] and HPS[23]; for diet,

Research Committee[24] and MRC Soya-Bean[25]; for fibrates and niacin, the Coronary Drug Project.[21]

[c] Data were missing for the GISSI-Prevention[22] statin trial; therefore, the number and percentage were calculated from the data presented in the other statin trials.

[d] The range was calculated from the mean or median LDL-C level presented in each individual trial. For the interventions with only 1 trial, there is only 1 number (no range), which is the mean (SD) from the individual trial.

[e] The mean was calculated from the mean or median presented in each trial.

between absolute reductions in LDL-C and lower RRs for major vascular events across therapies that ultimately work predominantly through upregulation of LDL receptor expression, such that each 1-mmol/L (38.7-mg/dL) reduction in LDL-C was associated with an RR of 0.77 (ie, 23% relative reduction) in the risk of major vascular events. There was also a significant linear association between achieved LDL-C and the rate of cardiovascular outcomes over the range of LDL-C studied.

The implications of these results deserve careful consideration in light of the strength of the available trial evidence for different types of therapies. As per current guidelines,[3,5] when tolerated, statins should be the first-line therapy given the large reductions observed for LDL-C, the excellent safety profile, the demonstrated clinical benefit, and low cost (now that most are generic). However, the data in the present meta-regression analysis raise the possibility that other interventions, especially those that ultimately act predominantly through upregulation of LDL receptor expression, may provide additional options and may potentially be associated with the same relative clinical benefit per each 1-mmol/L reduction in LDL-C. This analysis builds on prior observations in a smaller number of trials,[56,57] now expanded to several additional classes of therapy. These findings are also supported by Mendelian randomization studies showing a strong association between the degree of lower LDL-C imparted by a genetic variant and the magnitude of the lower cardiovascular outcome risk in carriers of that variant, irrespective of the gene.[58]

In addition to maximizing LDL-C reduction, cardiovascular risk assessment also remains a vital component of decision making because the absolute risk reduction in major vascular events achieved with an intervention will be a function of the RR reduction (which depends on the absolute

degree of LDL-C lowering) and the baseline risk of cardiovascular events. For example, a patient without known atherosclerotic cardiovascular disease who has a predicted risk of major vascular events of 15% and of hard cardiovascular events (cardiovascular death, MI, or stroke) of 10% within the next 10 years, lowering LDL-C level by 1 mmol/L (38.7 mg/dL) would be expected to result in absolute risk reductions of approximately 3.5% and 2.3%, respectively. A patient with known atherosclerotic cardiovascular disease who has a predicted risk of major vascular events of 45% and of hard cardiovascular events of 30% within the next 10 years, lowering LDL-C level by 1 mmol/L would be expected to result in absolute risk reductions of approximately 10% and 7%, respectively.

Niacin and fibrates reduced major vascular events in earlier trials, whereas more recent trials such as the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-Thrive),[59] the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD),[60] and the Action to Control Cardiovascular Risk in Diabetes (ACCORD)[61] failed to achieve a statistically significant reduction in their primary end points, calling into question the clinical utility of these drugs. However, the observed RR reduction in major vascular events was 4% (95% CI, −3% to 10%) in HPS2-Thrive, 11% (95% CI, 1% to 20%) in FIELD, and 8% (95% CI, −8% to 21%) in ACCORD, which were similar to the RR reductions predicted from the meta-regression (7%, 9%, and 0%, respectively). Based purely on LDL-C lowering and given the number of events accrued, the statistical power for their primary end points was only approximately 51% for HPS2-Thrive, 19% for FIELD, and 3% for ACCORD.

Ezetimibe was studied in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial[53] in patients receiving background statin therapy and

Figure 2. Association of Between-Group Difference in Achieved Low-Density Lipoprotein Cholesterol (LDL-C) Levels and Risk of Major Vascular Events
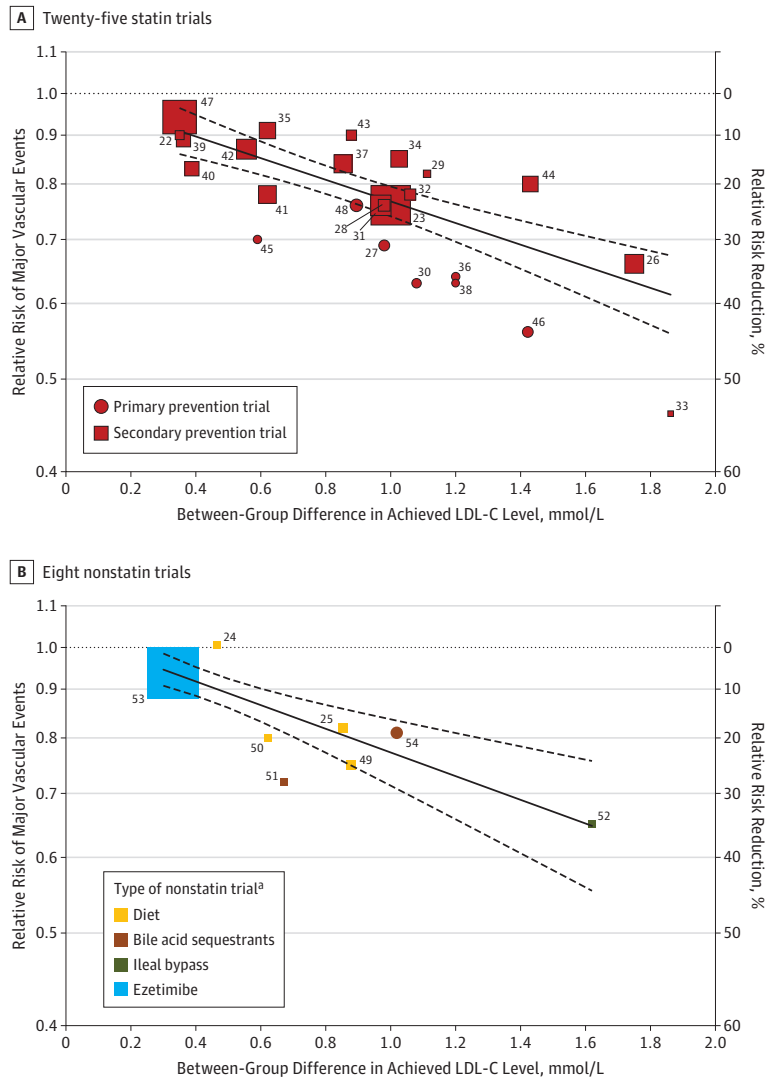
The LDL-C differences are either mean or median depending on what was presented for each trial. Major vascular events include cardiovascular death, acute myocardial infarction or other acute coronary syndrome, coronary revascularization, and stroke (eTables 1-5 in the Supplement provide additional details). The size of the data marker is proportional to the weight in the meta-regression. The meta-regression slope (predicted relative risk for degree of LDL-C reduction) is represented by the solid line and the 95% CIs by the dashed lines. To convert LDL-C from mmol/L to mg/dL, divide by 0.0259.

[a] The square data markers indicate secondary prevention trials. There was 1 primary prevention trial and 1 secondary prevention trial for bile acid sequestrants.

the RR reduction for major vascular events was 6.4% (95% CI, 1%-11%), with an absolute risk reduction of 2% over 7 years. The relatively small magnitude of the observed effect reflects the low starting LDL-C level by design that yielded a small absolute between-group difference, and is similar to what was predicted from our meta-regression (8.3%) and the Cholesterol Treatment Trialists' meta-regression of statin trials.[6] These results are also supported by genetic association and Mendelian randomization studies demonstrating similarly lower rates of cardiovascular outcomes per unit lower LDL-C in patients with loss-of-function variants in the Niemann-Pick C1-Like1 protein (the target of ezetimibe) and in HMG-CoA reductase (the target of statins).[62,63]

These data suggest that drugs that ultimately reduce LDL-C level predominantly through upregulation of LDL receptor expression should, barring any off-target adverse effects, lead to clinical benefit in proportion to the degree of LDL-C reduction.[64] This concept is further supported by

human genetic analyses of variants that have been associated with low LDL-C, increased LDL receptors, and decreased coronary heart disease.[58,62,63,65] In contrast, LDL-C reduction when not through increased clearance via the LDL receptor or by decreased production, does not necessarily translate into clinical benefit, as evidenced by the CETP inhibitor evacetrapib. In this case, the observed neutral result could have stemmed from a neutral effect of the LDL-C reduction due to the means by which it was lowered. However, the observed results could also stem from the expected benefit of LDL-C reduction being counterbalanced by an adverse effect of the drug. These observations underscore that large, long-term trials are ultimately necessary to provide adequate assurance for safety, and this also applies to the case of the PCSK9 inhibitors, which are currently under active investigation.

This analysis has limitations that warrant acknowledgment. First, the meta-analysis was not performed on patient-level data. However, beyond the logistical complex-

Figure 3. Weighted Between-Group Difference in Achieved Low-Density Lipoprotein Cholesterol (LDL-C) Level and Relative Risk for Major Vascular Events for Each Class of Intervention
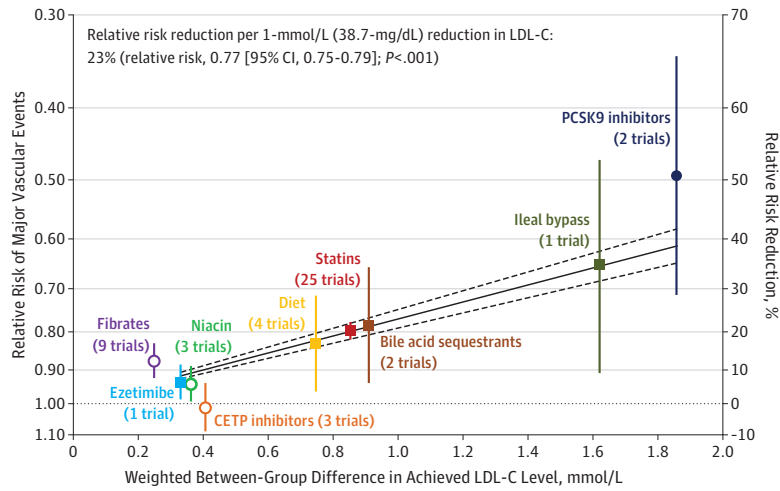
Each type of intervention is plotted based on the between-group difference in achieved LDL-C level (weighted across all the trials in the class) and the relative risk (with vertical lines depicting the 95% CIs) derived from meta-analysis of all trials in that class (eFigures 3-11 in the Supplement provide additional details). The square data markers indicate the established interventions that lower LDL-C predominantly through upregulation of LDL receptor expression.

The meta-regression slope (predicted RR for degree of LDL-C reduction) is represented by the solid black line and the 95% CIs by the dashed lines, both of which are derived from a trial-level analysis of all established interventions. To convert mmol/L to mg/dL, divide by 0.0259. CETP indicates cholesteryl ester transfer protein; PCSK9, proprotein convertase subtilisin/kexin type 9.

Figure 4. Association Between Achieved Low-Density Lipoprotein Cholesterol (LDL-C) and Major Coronary Event Rates From 24 Trials of Established Interventions That Lower LDL-C Predominantly Through Upregulation of LDL Receptor Expression
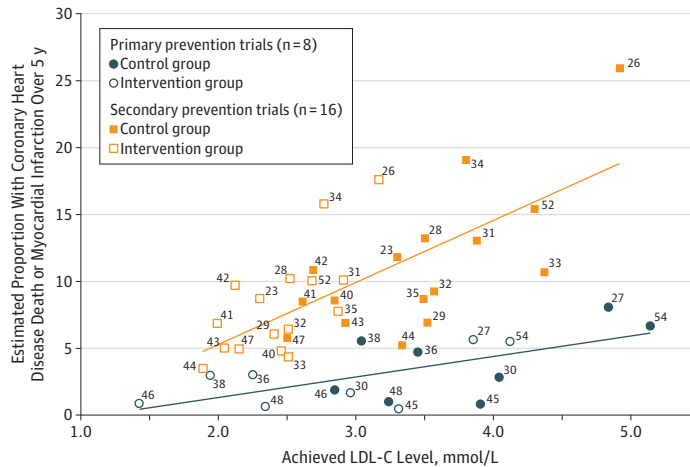
Levels of LDL-C are expressed as mean or median depending on what was reported in the trial. The solid lines are from meta-regression. To convert LDL-C from mmol/L to mg/dL, divide by 0.0259.

ity of gathering such data from 49 trials conducted over 51 years, by definition the analyses were at the trial level, examining the association between LDL-C reduction and the RR of major vascular events within a trial. Second, the absolute risk reduction observed in a given trial will depend in part on the patient population, the end point, and the duration of follow-up; therefore, the analysis was of relative rather than absolute risk. As noted above, clinicians would need to integrate the estimated RR reductions from these analyses with a patient's baseline risk to estimate the anticipated absolute risk reduction. Several tools are available for

estimating patient risk.[66-68] Third, the data for statins are more extensive than the data for other interventions, with more than 20 000 events from statin trials vs several thousand events each for ezetimibe, niacin, fibrates, and CETP inhibitor trials; several hundred events each for diet, bile acid sequestrants, and ileal bypass trials; and only 2 trials with 111 events during a mean follow-up of 1.2 years for the PCSK9 inhibitor trials. Fourth, the studies included in the analysis were conducted over a span of 51 years, and background therapy has changed, which may account for some of the difference in absolute event rates between trials.

Fifth, the components of the composite of major vascular events were not identical for every trial. Moreover, analysis of composite end points from trials precluded examining the association between LDL-C reduction and the RR of specific cardiovascular events. However, the effects of statins on the different elements of this composite end point have been shown to be largely consistent.[6] Sixth, hazard ratios were not available in all trials and risk ratios were used when they were not.

Conclusions

In this meta-regression analysis, the use of statin and nonstatin therapies that act via upregulation of LDL receptor expression to reduce LDL-C were associated with similar RRs of major vascular events per change in LDL-C. Lower achieved LDL-C levels were associated with lower rates of major coronary events.

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