Extent of Low-density Lipoprotein Cholesterol Reduction and All-cause and Cardiovascular Mortality Benefit: A Systematic Review and Meta-analysis

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Abstract: Lipid-modifying agents steadily lower low-density lipoprotein cholesterol (LDL-C) levels with the aim of reducing mortality. A systematic review and meta-analysis were conducted to determine whether all-cause or cardiovascular (CV) mortality effect size for lipid-lowering therapy varied according to the magnitude of LDL-C reduction. Electronic databases were searched, including PubMed and ClinicalTrials.gov, from inception to December 31, 2019. Eligible studies included randomized controlled trials that compared lipid-modifying agents (statins, ezetimibe, and PCSK-9 inhibitors) versus placebo, standard or usual care or intensive versus less-intensive LDL-C–lowering therapy in adults, with or without known history of CV disease with a follow-up of at least 52 weeks. All-cause and CV mortality as primary end points, myocardial infarction, stroke, and non-CV death as secondary end points. Absolute risk differences [ARD (ARDs) expressed as incident events per 1000 person-years], number needed to treat (NNT), and rate ratios (RR) were assessed. Sixty randomized controlled trials totaling 323,950 participants were included. Compared with placebo, usual care or less-intensive therapy, active or more potent lipid-lowering therapy reduced the risk of all-cause death [ARD −1.33 (−1.89 to −0.76); NNT 754 (529–1309); RR 0.92 (0.89–0.96)]. Intensive LDL-C percent lowering was not associated with further reductions in all-cause mortality [ARD −0.27 (−1.24 to 0.71); RR 1.00 (0.94–1.06)]. Intensive LDL-C percent lowering did not further reduce CV mortality [ARD −0.28 (−0.83 to 0.38); RR 1.02 (0.94–1.09)]. Our findings indicate that risk reduction varies across subgroups and that overall NNTs are high. Identifying patient subgroups who benefit the most from LDL-C levels reduction is clinically relevant and necessary.

Key Words: trial, number needed to treat, systematic review, meta-analysis, statins, ezetimibe, PCSK9-inhibiting monoclonal antibodies, low-density lipoprotein cholesterol

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INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD), a leading cause of morbidity and mortality, affects 423 million people and is responsible for 32% of all deaths worldwide.[1] Although it remains the most common cause of death in North America and Europe, deaths from ASCVD have declined substantially in the past 20 years,[2] due to improvements in risk factor management and medical treatment. Statins are considered the cornerstone of cardiovascular (CV) death reduction for both primary and secondary prevention.

Long-term exposure to excessive concentrations of low-density lipoprotein cholesterol (LDL-C) as in familial hypercholesterolemia is linked to premature atherosclerosis and early mortality. Epidemiological studies are conflicting.[3–5] After the failure of fibrates to reduce CV events, the 4S trial was the first to demonstrate a significant all-cause mortality reduction with simvastatin in a population of Northern European patients with coronary artery disease (CAD) with high baseline blood cholesterol.[6] For almost 30 years, a large number of randomized controlled trials (RCTs) have investigated the benefit of statin therapy and the addition of either ezetimibe or antiproprotein

convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies to statin therapy. Meta-analyses of LDL-C–lowering therapy found that event reduction correlates with the extent of LDL-C reduction.[7,8] Current guidelines recommend at least LDL-C 50% reduction and lower achieved LDL-C levels in high-risk patients.[9,10]

A comprehensive meta-analysis showed that mortality reduction was observed only in trials with mean baseline LDL-C level higher than 100 mg/dL, suggesting that the benefit from LDL-C–lowering therapy mostly occurs in patients with high baseline LDL-C levels.[11] In addition, all-cause mortality was not related to achieved targeted LDL-C levels.[11]

Because recent guidelines recommend larger LDL-C reduction to prolong life, we conducted an updated systematic review and meta-analysis of RCTs to determine whether the mortality effect size associated with lipid-lowering therapy varied according to the extent of LDL-C reduction. Patients were at risk for various CV conditions and followed for at least 1 year. The RCTs addressed the effectiveness of lipid-lowering therapy regarding absolute rate differences (ARDs) and thereby of the number of subjects needed to treat (NNT) for delaying the outcome beyond the study duration (NNT). The extent of LDL-C lowering for percentage or absolute reduction with the use of statins, ezetimibe, and PCSK-9–inhibiting monoclonal antibodies were extracted along with the reduction in all-cause and CV death risk. We also assessed CV events including myocardial infarction (MI) and stroke as well as non-CV death. Benefits of these therapeutics compared with the baseline and achieved LDL-C levels and also to the CV mortality rate of population studies were additionally evaluated.

METHODS

This systematic review included publicly available, previously published studies, and the meta-analysis was performed according to current guidelines,[12] complying with the *Preferred Reporting Items for Systematic review and Meta-Analysis* statement. The rationale and methods were prespecified in a protocol registered at PROSPERO (CRD42020144859).

Eligibility Criteria
Study Designs
Eligible studies included parallel-group or factorial RCTs. Observational cohort or retrospective case–control studies were not considered. RCTs enrolling more than 100 participants in each comparative group were included in the analysis.

Participants
RCTs enrolling adults with known or unknown ASCVD were included. Trials enrolling patients with left ventricular dysfunction, kidney disease, or aortic stenosis were included, as well as those with rheumatoid arthritis and chronic obstructive pulmonary disease.

Intervention
LDL-C–reduction therapy included statins, ezetimibe, and PCSK-9–inhibiting monoclonal antibodies.

Comparators
Less-intensive LDL-C reduction therapy included placebo of statin, ezetimibe, or PCSK-9–inhibiting monoclonal antibodies, usual care, and less potent or less-intensive statin therapy.

Outcomes
Primary studies were considered for eligibility when they reported at least 1 clinical outcome. Our primary outcomes were all-cause mortality and CV mortality. Secondary outcomes of interest were the number of MI events, stroke events, and non-CV mortality. These outcomes were assessed as ARDs and NNT related to the percent LDL-C reduction as primary analyses. Rate ratios (RR) were also provided as secondary analyses. We also assessed the risk reduction related to the absolute LDL-C–level reduction, baseline LDL-C levels, achieved LDL-C levels in the intervention group, and also according to the annual CV mortality rate in control arms.

Characteristics
Only primary studies with a mean or median follow-up duration of 12 months (ie, 52 weeks) or more were eligible. This time frame was based on the findings of previous trials.[13,14] Studies in English or French languages were included. All studies from inception to December 31, 2019 were included.

Information sources, search strategy, study selection, data extraction, data items, risk of bias assessment, and statistical analyses are provided in the **Supplemental Digital Content**(see, http://links.lww.com/JCVP/A874).

RESULTS

Study Identification
A flow chart describing the process of publication screening and reasons for exclusion is shown in (see **eFigure1**, Supplemental Digital Content, http://links.lww.com/JCVP/A874). We identified a total of 60 RCTs including 323,950 individuals. Among these, 162,393 patients were randomized to intensive LDL-C–lowering strategy and 161,557 were randomized to less-intensive strategy. The characteristics of the selected trials are shown in **Supplemental Digital Content** (see **eTables 1 and 2** and commented in the http://links.lww.com/JCVP/A874).

Characteristics of Included Studies
The **Supplemental Digital Content** (see **eTables 1 and 2**, http://links.lww.com/JCVP/A874) present the characteristics of the 60 eligible trials involving 323,950 participants (36 statins vs. placebo or usual care, 14 intensive statin vs. less-intensive statin, 5 PCSK9 inhibitors vs. placebo, 3 ezetimibe vs. placebo or usual care and 2 statin plus ezetimibe arm vs. double-placebo arm). Studies that enrolled patients with known and unknown ASCVD were referred to as secondary and primary prevention, respectively. Studies enrolling patients with specific conditions, including kidney disease, left ventricular dysfunction, chronic obstructive

pulmonary disease, previous stroke, and rheumatoid arthritis, were included in the meta-analysis. Eight studies used a factorial design, including a comparison between statin and placebo ALLHAT-LLT,[15] ASCOT-LLA,[16] PREVEND-IT,[17] HOPE-3,[18] ACAPS,[19] Post CABG,[20] HPS,[21] and GISSI-P.[22] In 1 trial, patients received ezetimibe monotherapy (EWTOPIA 75)[23]; statin and ezetimibe were given in in 4 trials (SEAS,[24] IMPROVE-IT,[25] HIJ-PROPER,[26] and SHARP[27]), statin and PCSK9-inhibiting monoclonal antibodies in 5 trials (ODYSSEY LONG TERM,[28] GLAGOV,[29] SPIRE-2,[30] FOURIER,[13] and ODYSSEY OUTCOME[14]), and LDL-C with therapeutic targets were compared in 2 trials (EMPATHY[31] and TST[32]). Twenty-four trials fail to reach statistical significance for the primary end point (PATE,[33] ALLHAT-LLT,[15] CERDIA,[34] PREVEND IT,[17] St Francis,[35] ASPEN,[36] SEAS,[24] STACOPE,[37] EMPATHY,[31] TRACE RA,[38] GISSI-P,[22] FLORIDA,[39] A-to-Z,[40] IDEAL,[41] SAGE,[42] SEARCH,[5] SATURN,[43] HIJ-PROPER,[26] CORONA,[44] GISSI HF,[45] ALERT,[46] GDDS,[47] AURORA,[48] and J-STARS.[49]) Sample size varied from 250 to 27,564 subjects. Eight trials were specifically conducted in Asia (PATE,[33] EMPATHY,[31] EWTOPIA,[23] MEGA,[50] HIJ PROPER,[26] J STARS,[49] REAL-CAD,[51] and Im et al [52]), 2 in Italy (GISSI-P[22] and GISSI-HF[45]), and 1 in Greece (GREACE[53]); most trials were conducted in North America, Northern Europe, and Oceania; of note, South Africa was virtually the only African Investigation site that was involved in 9 trials (ASPEN,[36] JUPITER,[54] HOPE-3,[18] IMPROVE-IT,[25] ODYSSEY LONG TERM,[28] GLAGOV,[29] SPIRE-2,[30] FOURIER,[13] and SPARCL[55]). The SEARCH trial had the longest mean follow-up (6.7 years).[56] The average follow-up was 3.93 ± 1.56 years. The mean weighted age for participants across primary studies was 63.2 years (range 49.7–80.6 years), and the mean weighted percentage of female participants was 30.1% (range, 0% to 74.5%). The mean weighted prevalence of active or history of cigarette smoking was 22.4% (range, 5% to 44%), hypertension 54.9% (range, 0% to 100%), and diabetes mellitus 24% (range, 0% to 100%). Of note, few black subjects were enrolled in the trials, and whites represented 69 ± 35% of the trial population (information available in 44 trials).

The mean weighted baseline LDL-C level was 121.2 mg/dL (range, 74.2 to 192 mg/dL) at baseline and 79.4 mg/dL (range, 30 to 165 mg/dL) at the end of the follow-up in the intervention group. Compared with the control group, the corresponding absolute and relative mean weighted LDL-C reduction were 36.8 mg/dL (range, 8 to 87 mg/dL) and 31.2% (range, 5 to 65 mg/dL) in the intervention group.

Outcomes

The (see **eTables 3–7, Supplemental Digital Content**, http://links.lww.com/JCVP/A874) are depicting the numbers of events in each group, which were used for the present meta-analysis. Potential sources of bias are listed in (see **eTable8, Supplemental Digital Content,** http://links.lww.com/JCVP/A874). Publication bias is shown by (see **eFigures 2–5, Supplemental Digital Content**, http://links.lww.com/JCVP/A874). The corresponding absolute risk

differences, NNTs, and RR pertaining to the extent of LDL-C reduction are shown in (**eTables 9–18, Supplemental Digital Content**, http://links.lww.com/JCVP/A875). Reassuringly, trends in RR and absolute rate differences were consistent for all outcomes and analyses.

Percentage LDL-C Reduction

All-cause Mortality

Fifty-eight studies reported the incidence of all-cause mortality. Pooled analysis showed that 12,965 of 161,551 patients (8.03%) receiving intensive LDL-C–lowering strategy versus 13,836 of 160,714 (8.61%) receiving less-intensive strategy died during follow-up [ARD −1.33 (−1.89 to −0.76); NNT 754 (529–1309); RR 0.92 (0.89–0.96)].

In unadjusted and adjusted meta-regression analyses, we did not find a significant trend toward decrease in both ARDs and RRs for all-cause mortality according to percentage LDL-C reduction (Fig. 1). In the meta-analysis by subgroups of baseline LDL-C level (Fig. 2), both all-cause mortality absolute and relative risks were reduced in the trials with <30% LDL-C reduction and those with 30%–49% LDL-C reduction, although risk reduction was not significant in trials with more than 50% LDL-C reduction [ARD −0.36 (−2.59 to 1.87); RR 0.99 (0.82–1.21) respectively].

Cardiovascular Mortality

Fifty-seven studies reported the incidence of CV mortality. Pooled analysis showed that 6631 of 159,494 patients (4.16%) receiving intensive LDL-C–lowering strategy versus 7394 of 158,659 (4.66%) receiving less-intensive strategy died of CV causes during follow-up [ARD −0.97
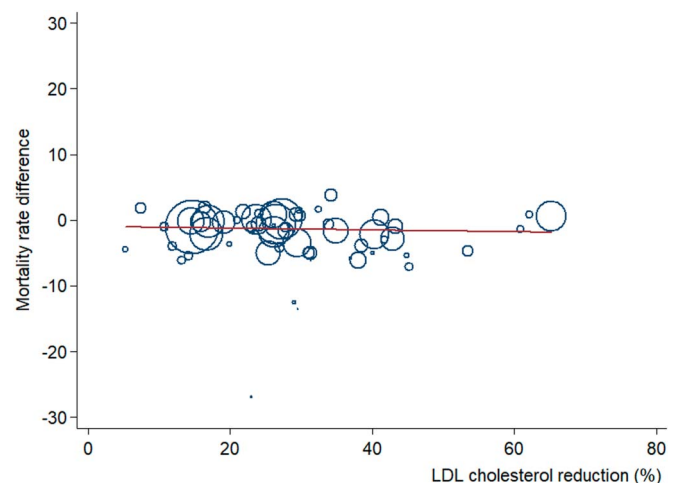
FIGURE 1. Meta-regression analysis of ARD in all-cause mortality risk by percent LDL-C level reduction. Change in ARD and 95% CIs of more intensive versus less-intensive LDL-C–lowering therapies plotted against percent LDL-C levels reduction. Size of the data markers is proportional to the weight in the meta-regression. The solid line represents the meta-regression slope of the change in ARD for treatment across increasing levels of percent LDL-C reduction.
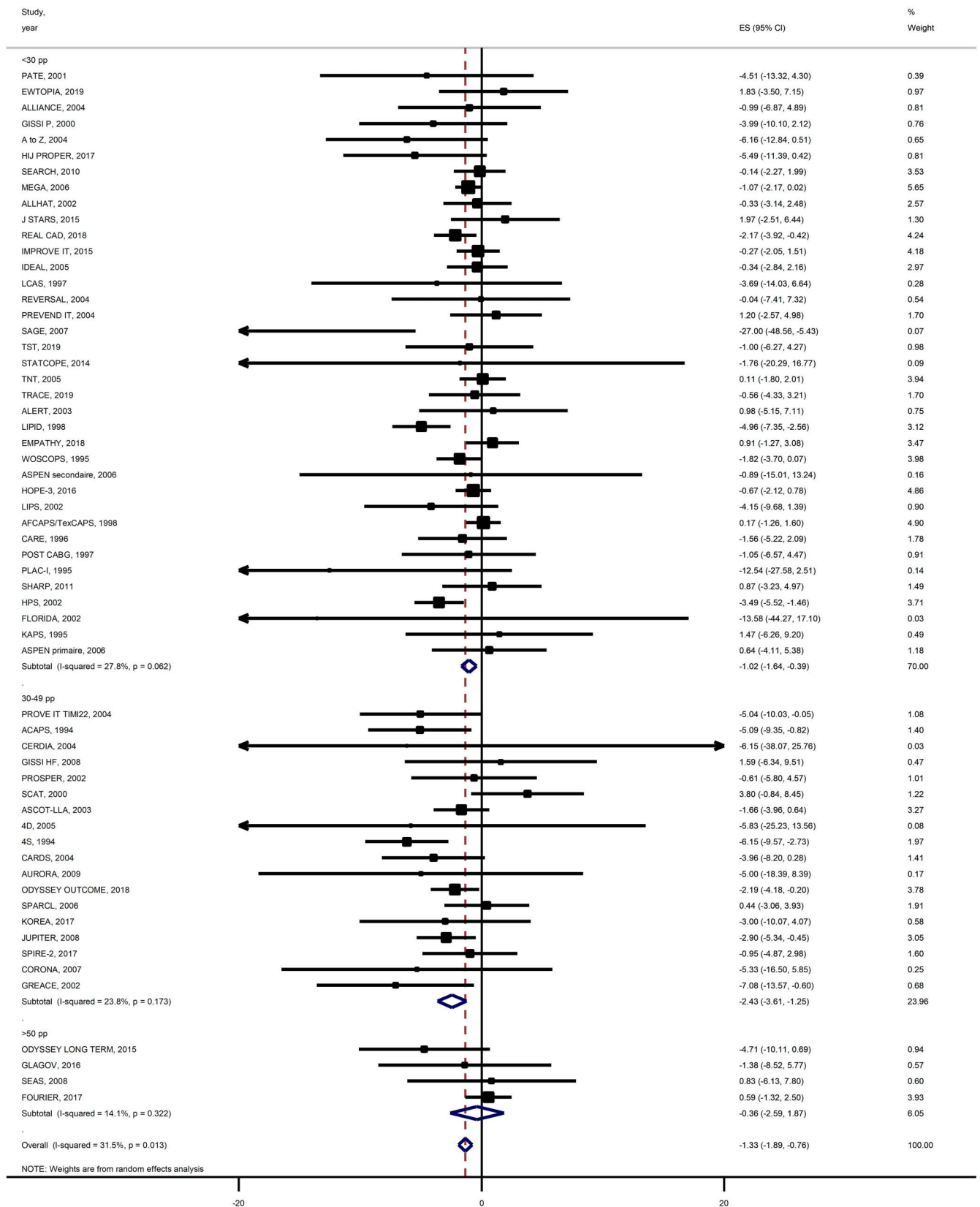
FIGURE 2. Meta-analysis of all-cause mortality risk stratified by percent LDL-C level reduction. ARD and 95% CIs of more intensive versus less-intensive LDL-C–lowering therapies and the weight of study data in the meta-analysis.

(−1.32 to −0.62); NNT 1028 (756–1605); RR 0.89 (0.85–0.92)].

In unadjusted and adjusted meta-regression analyses, for each 20% LDL-C reduction, intensive versus less-intensive LDL-C lowering was not associated with a change in ARDs or RRs for CV mortality (see **eFigure 7, Supplemental Digital Content**, http://links.lww.com/JCVP/A875). Similar to all-cause mortality, CV mortality relative and absolute risks were not reduced in pooled trials with ≥50% LDL-C reduction [ARD −1.03 (−3.23 to 1.17); RR 0.87 (0.63–1.22)] (see **eFigure 8, Supplemental Digital Content**, http://links.lww.com/JCVP/A875).

Myocardial Infarction

Fifty-five studies reported the incidence of MI. Pooled analysis showed that 7581 of 161,017 patients (4.71%) receiving intensive LDL-C–lowering strategy versus 9564 of 160,172 (5.97%) receiving less-intensive strategy experienced an MI during follow-up [ARD −2.76 (−3.33 to −2.18); NNT 363 (300–459); RR 0.77 (0.73–0.81)].

In both unadjusted and adjusted meta-regression, for each 20% LDL-C reduction, intensive versus less-intensive LDL-C lowering was associated with a change in ARDs ($P = 0.001$ to 0.002) for MI risk (see **eFigure 9, Supplemental Digital Content**, http://links.lww.com/JCVP/A875). Only after adjusted meta-regression analysis, including CV mortality rates, associated change was found when MI risk reduction was expressed in RRs ($P = 0.028$). In meta-analysis by subgroups, MI risk was further reduced in the pooled trials with more than 50% LDL-C reduction compared with those with 30%–49% and <30% reduction. This translated in high ARDs, low NNTs, and RRs in trials with high LDL-C reduction (see **eFigure10, Supplemental Digital Content**, http://links.lww.com/JCVP/A875).

Stroke

Fifty-three studies reported the incidence of stroke. Pooled analysis showed that 3483 of 160,295 patients (2.17%) receiving intensive LDL-C–lowering strategy versus 4285 of 159,438 (2.69%) receiving less-intensive strategy had a stroke during follow-up [ARD −1.1 (−1.45 to −0.76); NNT 907 (691 to 1319); RR 0.82 (0.77–0.87)].

In both unadjusted and adjusted meta-regression analysis, the ARDs for stroke risk increased significantly ($P = 0.003$ to 0.005) for each 20% LDL-C percentage reduction; a 9% increase in RRs for stroke was of borderline significance ($P = 0.05$ and 0.07 respectively) but a significant 13% increase after further adjustment to CV mortality rate ($P = 0.003$) (see **eFigure 11, Supplemental Digital Content**, http://links.lww.com/JCVP/A875). Like with mortality, RR and ARD were not significant in the trials with more than 50% LDL-C reduction (see **eFigure 12, Supplemental Digital Content**, http://links.lww.com/JCVP/A875).

Additional analyses (see **Supplemental Digital Content**, http://links.lww.com/JCVP/A875) including those for absolute LDL-C reduction (see **eTables 9 and 10, Supplemental Digital Content**, http://links.lww.com/JCVP/A875), baseline LDL-C levels (see **eTables 13,** 14 and **eFigures 13–16, Supplemental Digital Content**, http://links.lww.com/JCVP/A875), and achieved LDL-C levels (see **eTables 15, 16** and **eFigures 17–22, Supplemental Digital Content**, http://links.lww.com/JCVP/A875) as well as for non-CV mortality are shown in the Supplement. The association between CV mortality rates of studied populations and outcomes were also studied (see **eTables 17, 18** and **eFigures 23–26, Supplemental Digital Content**, http://links.lww.com/JCVP/A875).

DISCUSSION

The purpose of this systematic review and meta-analysis was to determine whether all-cause or CV mortality effect size for lipid-lowering therapy varied according to the magnitude of LDL-C reduction. Our findings indicate that all-cause and CV mortality reduction was not related to LDL-C relative or absolute reduction (RR and ARD) or to baseline and achieved LDL-C levels in meta-regression models. In trials with LDL-C lowering above 50% and in those with baseline LDL-C levels below 130 mg/dL, all-cause and CV mortality benefits were not consistent and clinically relevant both for absolute and relative risk reduction. Overall, MI risk was reduced but mostly in trials with LDL-C reduction above 50% or 65 mg/dL and in trials with high baseline LDL-C levels. The relationship between achieved LDL-C levels and MI risk was not apparent from our findings. The benefit on stroke risk was not evident with percentage reduction above 50% or when absolute LDL-C reduction was more than 65 mg/dL. The annual NNTs were overall high. The lowest annual NNTs (129–187) were found in trials with high relative or absolute LDL-C reduction and those with the highest baseline LDL-C levels for the risk of MI. Furthermore, our findings do not support a clear relationship between lowering LDL-C achieved levels and events reduction. Achieving LDL-C level below 55 mg/dL did not translate in further significant all-cause and CV mortality benefit.

Several meta-analyses have found consistent event reduction with lipid-lowering therapies. The CTT collaboration reported that a 1.0-mmol/L (38.7-mg/dL) LDL-C reduction was associated with a 10% reduction [RR 0·90, 95% confidence interval (CI), 0.87–0.93; $P < 0.0001$] and significant mortality reductions from CAD (RR 0.80, 99% CI, 0.74–0.87; $P < 0.0001$) and other cardiac causes (RR 0·89, 99% CI, 0.81–0.98; $P = 0.002$)[8]; Silverman et al[7] found that the relative risk reduction for major vascular events per absolute 1-mmol/L (38.7-mg/dL) reduction in LDL-C level was 0.77 (95% CI, 0.71–0.84; $P < 0.001$) for statins.

The latest European Society of Cardiology guidelines recommend LDL-C reduction of ≥50% from baseline and lower LDL-C goal below 55 mg/dL in extremely high-risk patients whether for primary or secondary prevention and below 40 mg/dL in those with a second vascular event within 2 years, while taking maximally tolerated statins.[9] A LDL-C reduction of ≥50% from baseline and a LDL-C goal of <70 mg/dL are recommended in patients at high CV risk. A LDL-C target of <100 mg/dL is recommended in patients at moderate CV risk, whereas a target of <116 mg/dL should be targeted for low-risk individuals. However, the benefits of

these lower LDL-C goals have not been formally demonstrated in patients previously treated with lipid-lowering agents and are derived from meta-analyses and from trials, including PCSK-9 inhibition added to statin and ezetimibe, occurring in the past 30 years. Indeed, past meta-analyses mixed a variety of populations treated differently. In the 4S RCT, for instance, 37% of randomized Scandinavians received aspirin and only 7% had not benefited from revascularization therapy,[6] whereas the use of secondary preventive therapies was utmost in patients enrolled in the FOURIER RCT.[13] When considering high-risk patients with mean baseline LDL-C levels of 190 mg/dL enrolled in 4S[6] or WOSCOPS[57] trials, the target of 55 or even 40 mg/dL requires lipid-lowering therapy to reduce LDL-C by 70%–80% (135–150-mg/dL in absolute reduction). This strategy needs to be prospectively demonstrated with adequately powered trials.

All-Cause and Cardiovascular Mortality End points

All-cause mortality is the less equivocal end point; only 2 early seminal trials (4S[6] & HPS[21]) were individually positive for mortality as primary end point and a limited number of trials, including LIPID,[58] GREACE,[53] JUPITER,[54] REAL CAD,[51] and ODYSSEY OUTCOME,[14] showed mortality reduction with intensive lipid-lowering therapy in a secondary end point analysis. Adjudication of CV mortality may be controversial even in prospective clinical trials; however, our findings on CV mortality were consistent with those of all-cause mortality and the association was not present in patients who experience high LDL-C relative reduction. Aggressive management of CV events currently may account for the lack of mortality benefit and even more so when LDL-C percentage reduction was greater than 50%. The short duration of RCTs and the limited number of RCTs showing the highest LDL-C reductions may also explain wider CIs and lack of mortality benefit.[13] The present meta-analysis also concurs with main findings of Navarese et al.[11] All-cause and CV mortality risks were not substantially lowered when baseline LDL-C levels were below 130 mg/dL for ARDs and RRs. For both end points, mean NNTs were high, suggesting a questionable individual mortality benefit. Despite the limited value of information from observational epidemiological studies about treatment effects, it is worthy to note that in the Cooper Center Longitudinal Study, only LDL-C categories of ≥160 mg/dL remained independently associated with CV mortality.[59] By contrast, risk of all-cause mortality did not increase substantially between LDL-C categories <100 mg/dL, 100 to 129 mg/dL, 130 to 159 mg/dL, 160 to 189 mg/dL, and ≥190 mg/dL.[59]

Myocardial Infarction and Stroke End points

These end points are less robust for meta-analyses because the definition of MI has evolved with the continuous development of high-sensitivity cardiac injury biomarkers. In the seminal 4S trial, "major coronary events" comprised coronary deaths, definite or probable hospital-verified nonfatal acute MI, resuscitated cardiac arrest, and definite silent MI verified by major Q-wave pattern changes on electrocardiogram.[6] Three decades ago, creatine kinase and its MB isoenzyme (CK-MB) were commonly used for the diagnosis of MI. In the ODYSSEY Outcomes trial, MI was defined in accordance with ACC/AHA/ESC universal definition of MI with the use of cardiac troponin I or T.[60] As a result, MI prevalence in the 4S trial will differ with the use of high-sensitivity cardiac troponin. The lowest NNTs (high therapeutic impact) to postpone MI were observed with highly intensive LDL-C relative or absolute reduction and high baseline LDL-C levels; however, mean annual NNT numbers still remained above 100. Of note, Navarese et al [11] reported similar findings with an RR of 0.84 when baseline LDL-C levels were less than 100 mg/dL and 0.64 for baseline LDL-C levels greater than 160 mg/dL.

Similarly, lipid-lowering therapy aims at reducing atherothrombotic nonhemorrhagic stroke, whereas stroke may include embolic, nonembolic, and cryptogenic ischemic stroke as well as hemorrhagic stroke unrelated to cerebral infarction. Over time, the increasing use of brain magnetic resonance imaging, CT angiography, transesophageal echocardiogram with bubble study, or ambulatory electrocardiogram also refined the diagnosis of atherosclerotic strokes. The number of unclassified strokes was substantial in the 4S trial.[6] These specific issues may explain why the present findings are at variance with previous reports. Nevertheless, the RR of 0.82 reported by Navarese et al[11] equals that of the present investigation. In addition, the benefit for stroke did not vary with baseline LDL-C levels in both studies and became nonsignificant within the trials with the highest LDL-C reductions (more than 50% or 65 mg/dL reduction). The high mean NNTs were overall noted for end point stroke risk reduction. It is worthy to note that in contrast to the relationship between MI risk and blood cholesterol, the association between spontaneous cholesterol levels and stroke risk was found weak or nonexistent in large epidemiologic studies.[61,62] Indeed, the 2 large trials aimed at demonstrating LDL-C lowering after atherosclerotic stroke, SPARCL[55] and TST[32] showed small absolute benefits and high NNTs; the Japanese J-STARS[49] trial was neutral. Of note, a 20% and 60% (atorvastatin 80 mg) increase in hemorrhagic stroke per mmol/L LDL-C reduction was reported in the CTT meta-analysis[8] and SPARCL trial,[55] respectively.

General Comments

The NNT offers a better appreciation of the clinical relevance of treatment benefit and thereby helps improved clinical decision making at the individual level. The NNT derives directly from the absolute benefit, which is the difference in the observed rates of events in the treated and control groups over a fixed period. The greater the absolute benefit, the smaller the NNT. Although relative risk or rate reduction remains constant or increases in low-risk patients, absolute benefit drops to small numbers and NNTs raise to large numbers. Like hazard ratios, RR may overstate the benefits in populations with low event rates while the NNT rises. For instance, previous meta-analyses found a relative risk reduction of 38% (RR 0.62) in patients with 5-year event risk of <5% and a 21% risk reduction in those with a 5-year risk of >30%, although absolute risk reductions were opposed (0.18% in low-risk and 1.18% in high-risk patients).[63] Such data presentation may mislead clinicians.

Similarly, Wang et al[64] found that risk reduction of major vascular events is independent of the starting LDL-C; however, the ARD was 0.5% in studies with baseline LDL-C less than 100 mg/dL but 1.2% in studies with baseline LDL-C more than 158 mg/dL. Recently, Yourman et al [65] reported that treating 100 adults aged >55 years without known CV disease with a statin for 2.5 years prevented 1 CV event in 1 adult without mortality benefit.

Risk-based intervention strategies recommended by guidelines suggest that the higher baseline CV risk, the greater the absolute reduction in risk.[10] Only CV mortality absolute risk reduction was tightly related to CV mortality rates, whereas for both MI and stroke end points, annual CV mortality rates did not relate to the extent of benefits in absolute risk reduction. Of note, significant meta-regressions between percent LDL-C reduction and MI or stroke absolute risk reduction (see **eTable 8**, **Supplemental Digital Content**, http://links.lww.com/JCVP/A874) or between absolute LDL-C reduction and MI or stroke relative risk reduction (see **eTable 10**, **Supplemental Digital Content**, http://links.lww.com/JCVP/A875) emerged only after adjustment on CV mortality rates.

Large NNTs suggest that the "one size fits all" approach is not recommended for the future of precision medicine and may not be adapted to a constraint health care economy.[65] Benefits found with LDL-C–lowering therapies are indeed modest when compared with the benefits of timely myocardial revascularization in acute MI, antithrombotic therapy, therapies aimed at left ventricular dysfunction, smoking cessation, regular exercise, and obesity prevention.[66–69]

Short duration or early termination in recent trials including ASCOT-LLA,[16] CARDS,[70] JUPITER,[54] or FOURIER[13] may account for the lack of mortality benefit despite large randomized populations. Short follow-up duration might also account for the discrepancy between MI benefit and mortality benefit in trials with more than 50% LDL-C reduction or low baseline LDL-C levels. Alternatively, premature trial termination may also have overestimated benefits of the lipid-lowering strategy.[71]

Although the choice of major adverse cardiac events as an end point reduced the NNTs, they were nevertheless 67 (147 per year) in FOURIER[13] and 49 (137 per year) in ODYSSEY OUTCOME trial.[14]

Limitations

The study did not solely consist of published trials that had prespecified clinical outcomes. Other data besides primary and secondary end points may not have been rigorously and consistently recorded. Some outcomes, such as stroke and MI, resulted in imprecise estimates of effects and low certainty evidence. The present meta-analysis only considered trials with the required data; thus, it made it challenging to compare trials for specific differences. We did not address the specific impact of respective lipid-lowering drugs. Limitations include heterogeneity in clinical settings of the trials. Lipid lowering is indeed prescribed in a vast proportion of the population to prevent ASCVD. Our findings might be confounded by various comorbid conditions, such as rheumatoid arthritis. Yet they were reported

inconsistently and could not be extracted from primary study reports. In addition, mixing trials that investigated lipid-lowering strategies for primary and secondary prevention may somewhat weaken the present meta-analysis. However, vascular benefits of statin therapy were demonstrated in large meta-analyses mixing primary and secondary prevention trials.[8,64,72] Conversely, an unknown proportion of patients who were enrolled in primary prevention trials had silent ASCVD, significant plaque on coronary or carotid artery or target organ damage, and may be viewed today as being at a higher risk. Recent LDL-C goals along with CV risk categories released by the latest guidelines illustrate this strategy.[9]

LDL-C may not be the best risk predictor of CV mortality/events as small dense LDL-C phenotype or as non-HDL-C.[9,73] However, these data were not consistently available from all trials. Moreover, guidelines largely focus on the simple LDL-C parameter, whereas ESC guidelines state that there is "compelling evidence that LDL-C is causally associated with the risk of ASCVD, and that lowering LDL-C reduces the risk of ASCVD proportionally to the absolute achieved reduction in LDL-C."

The ARD and NNT are influenced by the baseline risk for disease and amount of time at risk, although the RR is theoretically not affected. Nevertheless, impressive RRs may mask low ARDs especially in control groups with low event rates, as previously discussed.

Benefits of LDL-C–lowering therapy may accrue over time, causing the NNT to become much lower over longer periods. By contrast, mortality may become similar after trial's termination.[74]

Empirical evidence suggests that meta-analysis of difference measures (rate and risk differences) are prone to heterogeneity, although this observation may relate to statistical power favoring heterogeneity tests on difference versus relative effect measure scale.[75,76]

CONCLUSIONS

The present meta-analysis confirms that LDL-C–lowering therapy statistically reduces mortality. The meta-regressions and meta-analyses by subgroups indicate that LDL-C lowering may not be beneficial for all-cause and CV mortality end points in trials with more than 50% LDL-C reduction and in trials with low baseline LDL-C levels. By contrast, the reduction in MI risk was consistent across all analyses. However, annual NNTs were overall relatively high, and trials enrolling patients with high baseline LDL-C levels reported the most benefit from LDL-C–lowering therapy especially for MI. Achieving lower LDL-C goals did not further increase risk reduction consistently. Uncovering subgroups of patients who derive the most benefits from LDL-C levels reduction remains clinically relevant.

WHAT IS ALREADY KNOWN ON THIS TOPIC

A large number of meta-analyses have found indiscriminate benefits of LDL-C reduction on mortality and CV events.

WHAT THIS STUDY ADDS

Trials reducing LDL-C more than 50% did not consistently further decrease all-cause and CV mortality; the reduction in MI risk was consistent across all analyses.

Mortality benefits were found within trials with baseline LDL-C levels more than 130 mg/dL.

Achieved LDL-C levels were not related to mortality reductions.

Overall annual NNTs were relatively high, thereby uncovering subgroups of patients who benefit the most from LDL-C levels reduction is clinically relevant.

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