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Short Report

Cardiovascular mortality after intensive LDL-Cholesterol lowering: Does baseline LDL-Cholesterol really matter?

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ABSTRACT

It remains controversial whether reductions in cardiovascular mortality after intensive lowering of low density lipoprotein cholesterol (LDL-C) depend on baseline LDL-C levels. To reassess these findings, in this brief report, we performed an updated literature search through February 2020 and selected randomized controlled trials which reported cardiovascular mortality and major adverse cardiovascular events (MACE) as outcomes. We included 53 randomized controlled trials (329,897 patients) of LDL-C lowering therapies (statin, ezetimibe and PCSK9 inhibitors) and stratified the meta-analysis according to the baseline LDL-C thresholds. Our meta-analysis found that each 38.7 mg/dL (1 mmol/L) lowering in LDL-C reduced the risk of cardiovascular mortality (RR, 0.85; 95% CI, 0.81–0.89), but this varied by baseline LDL-C of those in the trials ($P = 0.04$ for interaction). The risk reduction in cardiovascular mortality was limited to trials with baseline LDL-C of >100 mg/dL. In contrast, the reduction in MACE was independent of baseline LDL-C levels. These findings were consistent in primary and secondary prevention settings for both outcomes and by sex for MACE. Our results support the professional cholesterol guidelines which recommend achieving a $\geq 50\%$ reduction in LDL-C from baseline for high-risk patients.

Introduction

Low density lipoprotein cholesterol (LDL-C) is a well-established modifiable risk factor for atherosclerotic cardiovascular disease [1–3]. While current American Heart Association (AHA)/American College of Cardiology (ACC)/Multi-society and European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) cholesterol guidelines suggest different therapeutic goals for LDL-C, both professional guidelines recommend intensive lowering of LDL-C level for secondary prevention and high risk primary prevention [1,2].

The Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis of statin therapy showed a consistent relative risk (RR) reduction in major vascular events per 1 mmol/L (38.7 mg/dL) LDL-C reduction that was independent of baseline LDL-C levels [4]. These findings were also shown in a recent meta-analysis by Wang and colleagues, who concluded that RR reduction in major vascular events per 1 mmol/L reduction in LDL-C was independent of starting LDL-C levels, or other risk factors such as diabetes or chronic kidney disease [5]. Wang et al. abstracted primary endpoints from trials that closely approximate a composite of cardiovascular mortality, myocardial infarction or acute

coronary syndrome, stroke and coronary revascularization. Although similar methods have been previously used [6], this approach is not ideal given substantial heterogeneity in the definition of primary endpoint across the trials. Moreover, since the authors did not perform a meta-analysis of the individual components of the primary outcome, the influence of individual cardiovascular endpoints on the results remains uncertain.

The most important issue is the influence of baseline LDL-C on cardiovascular mortality after intensive LDL-C reduction. Navarese et al. reported that intensive LDL-C lowering reduced the risk of major adverse cardiovascular events (MACE), independently of baseline LDL-C [7]. However, cardiovascular mortality benefit was limited to trials with baseline LDL-C >100 mg/dL. Similar findings were noted in another meta-analysis of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors [8].

To reassess these findings, in this brief research report, we performed an updated meta-analysis of the benefits of LDL-C lowering therapy on cardiovascular mortality by baseline LDL-C concentrations. We hypothesized that while MACE reduction per 38.7 mg/dL lowering in LDL-C by LDL-C lowering therapy would be independent of baseline LDL-C levels,

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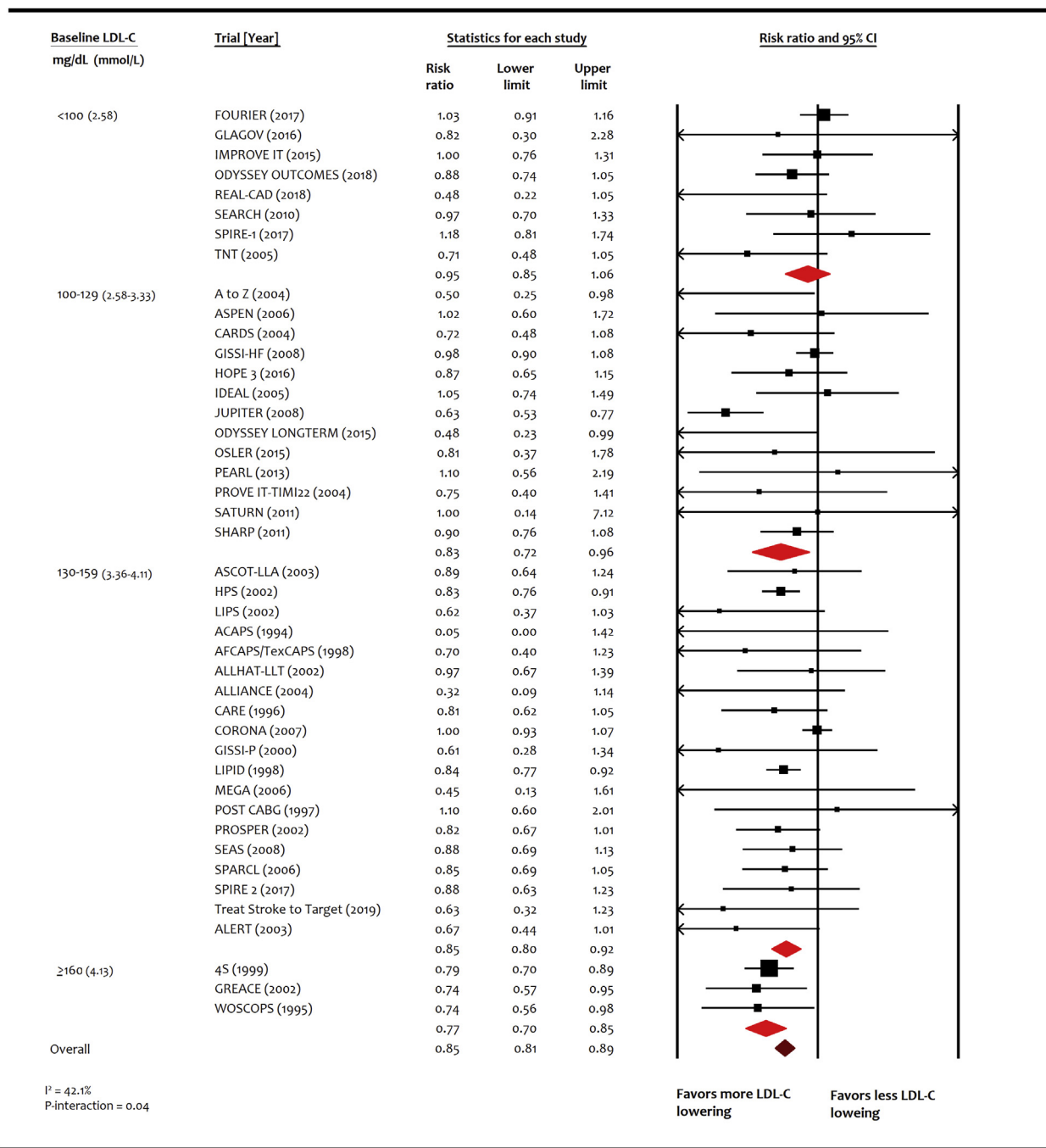


Fig. 1. Relative Risk of Cardiovascular Mortality per 38.7 mg/dL reduction in LDL-C, by baseline LDL-C Concentration Squares represent individual studies, with the size proportional to the weight in the meta-analysis. Diamonds represent pooled results.

that the cardiovascular mortality risk reduction would be exclusively limited to patients with LDL-C >100 mg/dL. Our secondary hypothesis was that cardiovascular risk reduction in patients >100 mg/dL would be consistent across sex and setting (primary vs secondary prevention).

Methods and results

We performed an updated literature search through 02/02/2020 and selected randomized controlled trials which reported cardiovascular mortality and MACE. We included 53 randomized controlled trials (329,897 patients) of LDL-C lowering therapies (statin, ezetimibe and PCSK9 inhibitors). Data were abstracted on drugs, baseline LDL-C and mean LDL-C reduction achieved in the trial, sex-specific estimates and the

type of patients enrolled in trials (primary, secondary or both). Since cardiovascular mortality was not primary endpoint in component trials of this meta-analysis, sex-specific data were only available for MACE. Twenty trials were conducted in secondary prevention setting, 12 trials in primary prevention and 19 trials enrolled mixed cohort. Meta-analysis was stratified according to the baseline LDL-C thresholds [7]. We standardized the analysis to 38.7 mg/dL reduction in LDL-C by taking log summary statistic of each trial and multiplying it by 1/d, where d refers to the mean LDL-C reduction (mg/dL) in the trial [5].

Our meta-analysis showed that each 38.7 mg/dL in LDL-C reduced the risk of cardiovascular mortality [Risk Ratio (RR), 0.85; 95% confidence interval (CI), 0.81–0.89], but this varied by baseline LDL-C of those in the trials. The risk reduction in cardiovascular mortality was limited to trials

Table 1

Subgroup analysis of outcomes per 38.7 mg/dL reduction in low density lipoprotein cholesterol in trials with baseline LDL-C >100 mg/dL.

| Subgroup | Cardiovascular mortality | MACE |
|----------------|--------------------------|-------------------|
| Setting | | |
| Primary | 0.79 [0.69, 0.90] | 0.74 [0.69, 0.80] |
| Secondary | 0.86 [0.80, 0.92] | 0.80 [0.77, 0.83] |
| P-interaction | 0.29 | 0.06 |
| Sex | | |
| Men | – | 0.81 [0.77, 0.86] |
| Women | – | 0.85 [0.80, 0.90] |
| P-interaction | – | 0.28 |

with baseline LDL-C of >100 mg/dL ($P = 0.04$ for interaction; Fig. 1). On the other hand, the reduction in MACE was independent of baseline LDL-C levels. Each 38.7 mg/dL lowering in LDL-C reduced the RR of MACE by 0.80 (95% CI, 0.77–0.83), which was consistent in trials with baseline LDL-C <100 mg/dL (0.83, 95% CI, 0.76–0.90), 100–129 mg/dL (0.77, 95% CI, 0.69–0.85), 130–159 mg/dL (0.82, 95% CI, 0.78–0.86) or ≥ 160 mg/dL (0.78, 95% CI, 0.75–0.82) ($P = 0.49$ for interaction). Subgroup analysis in trials with baseline LDL-C >100 mg/dL showed that RR reductions in cardiovascular mortality and MACE were consistent across primary or secondary prevention trials, or sex in case of MACE (Table 1).

Discussion

Reduction in cardiovascular mortality depends on several factors, including large absolute LDL-C reduction, long-term follow-up, high-risk patients, therapeutic efficacy of the drug and minimal or no competing risk or off target effects [6–8]. Therefore, patients starting with a baseline LDL-C >100 mg/dL have a stronger signal for mortality reduction, as they would be expected to have a larger absolute reduction in LDL-C [6–8]. This concept was consistently shown across various clinical trials of lipid lowering therapy. For instance, in earlier PCSK9 inhibitor trials, ODYSSEY LONG TERM and OSLER showed numerically lower mortality rates in participants with baseline LDL-C levels of ~ 120 mg/dL [9,10]. In the recent ODYSSEY OUTCOMES trial, the absolute risk reduction in primary endpoint was most pronounced in patients with baseline LDL-C >100 mg/dL [11]. There was also a 15% RR reduction in all-cause mortality among patients with recent acute coronary syndrome receiving alirocumab. However, because of pre-specified hierarchical testing of secondary endpoints, the reduction in all-cause mortality was considered a nominal finding in the absence of cardiovascular mortality. Similarly, among trials of statin therapy, the 4S trial showed a 29% RR reduction in all-cause mortality in patients with starting LDL-C level of 188.3 mg/dL [12]. In GREACE, there was 43% RR reduction in patients with baseline LDL-C of 180 mg/dL [13]. Similar findings were noticed in other trials, such as the PROVE-IT TIMI 22, LIPID and HPS trials [14–16].

The findings may also potentially explain the lack of mortality benefit in the FOURIER (baseline LDL-C = 92 mg/dL) and IMPROVE-IT (baseline LDL-C = 93.8 mg/dL) trials, where despite achieving very low levels of LDL-C, evolocumab and ezetimibe (plus statin therapy), respectively, did not reduce the risk of cardiovascular or all-cause death [17,18]. Of note, an important limitation of PCSK9 inhibitor trials in reducing mortality was relatively shorter follow-up duration compared with statin trials. A comparative analysis of CTTC meta-analysis of statin therapy and FOURIER and SPIRE trials showed that the magnitude of cardiovascular risk reduction achieved by PCSK9 inhibitor was similar to what would have been expected up to two years, signaling that beneficial effects of therapy potentiates over time [19,20].

In summary, consistent with prior reports [7,8], we argue that while the effect of intensive LDL-C lowering on a MACE endpoint might be independent of starting LDL-C levels, the mortality benefit is most likely restricted to patients with higher baseline LDL-C levels. These findings refute the impression of CTTC meta-analysis or study by Wang and

colleagues, which suggest that patients at lower cardiovascular risk might have similar RR reduction with LDL-C lowering therapies [4,5]. In fact, our results support the professional cholesterol guidelines which recommend achieving a $\geq 50\%$ reduction in LDL-C from baseline for high-risk patients.

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Declaration of competing interest

No conflicts of interest.

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