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ORIGINAL RESEARCH ARTICLE

# Benefits and Risks of Antihyperlipidemic Medication in Adults with Different Low-Density Lipoprotein Cholesterol Based on the Number Needed to Treat

**Hong-Fei Wang[1,2] · Yu-Cheng Mao[1,2] · Su-Fen Qi[1,2] · Xin-Yi Xu[3,4] · Zi-Yan Zhang[1,2] · Chang Geng[1,2] · Kai Song[1,2] · Qing-Bao Tian[1,2]**

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## Abstract

**Purpose** The objective of this investigation is to examine the benefits and potential risks of these drugs in individuals by varying baseline low-density lipoprotein cholesterol (LDL-C) values, utilizing the concept of the number needed to treat (NNT).

**Methods** We extensively searched electronic databases, such as PubMed, EMBASE, Cochrane, and Web of Science, up to 6 August 2023. Baseline LDL-C values were stratified into four categories: < 100, 100–129, 130–159, and ≥ 160 mg/dL. Risk ratios (RRs) and NNT values were computed.

**Results** This analysis incorporated data from 46 randomized controlled trials (RCTs), encompassing a total of 237,870 participants. The meta-regression analysis demonstrated an incremental diminishing risk of major adverse cardiovascular events (MACE) with increasing baseline LDL-C values. Statins exhibited a significant reduction in MACE [number needed to treat to benefit (NNTB) 31, 95% confidence interval (CI) 25–37], but this effect was observed only in individuals with baseline LDL-C values of 100 mg/dL or higher. Ezetimibe and PCSK9 inhibitors also were effective in reducing MACE (NNTB 18, 95% CI 11–41, and NNTB 18, 95% CI 16–24). Notably, the safety outcomes of statins and ezetimibe did not reach statistical significance, while the incidence of injection-site reactions with PCSK9 inhibitors was statistically significant [number needed to treat to harm (NNTH) 41, 95% CI 80–26].

**Conclusion** Statins, ezetimibe, and PCSK9 inhibitors demonstrated a substantial capacity to reduce MACE, particularly among individuals whose baseline LDL-C values were relatively higher. The NNT visually demonstrates the gradient between baseline LDL-C and cardiovascular disease (CVD) risk.

**Systematic Review Registration** Registration: PROSPERO identifier number: CRD42023458630.

## 1 Introduction

Atherosclerotic cardiovascular disease (ASCVD) imposes substantial global health and economic burdens [1]. Low-density lipoprotein cholesterol (LDL-C) level is one of

**Key Points**

The number needed to treat (NNT) is a crucial tool in visualizing benefits and risks, aiding hyperlipidemia patient management.

Statins, ezetimibe, and PCSK9 inhibitors significantly reduce MACE, with increasing NNT as LDL-C values rise.

Statins and ezetimibe safety are not significant; PCSK9 inhibitors show notable injection-site reactions.

✉ Qing-Bao Tian
tqb1980@hebmu.edu.cn

1 Department of Epidemiology and Statistics, School of Public Health, Hebei Medical University, Shijiazhuang, China

2 Hebei Key Laboratory of Environment and Human Health, Shijiazhuang, China

3 Postdoctoral Research Station in Basic Medicine, Hebei Medical University, Shijiazhuang, China

4 School of Nursing, Hebei Medical University, Shijiazhuang, China

the established risk factors. The cornerstone strategy for preventing both primary and secondary ASCVD revolves around the reduction of LDL-C [2]. The 2018 American College of Cardiology and American Heart Association (ACC/AHA) cholesterol guidelines recommended the employment of LDL-lowering drugs, including statins, as well as non-statins such as ezetimibe and PCSK9 inhibitors [3]

Notably, a recent meta-analysis by the Cholesterol Treatment Trialists (CTT) showed that each 1 mmol/L decrease in LDL-C corresponded to a 15% proportional reduction in the risk of occlusive vascular events, irrespective of baseline LDL-C [2]. Furthermore, it is worth highlighting that the clinical benefit in the context of cardiovascular events becomes pronounced as the extent of LDL-C reduction increases [4]. Another investigation has suggested that individuals with higher baseline LDL-C values would derive more substantial benefits from this reduction [5].

These studies have primarily focused on the concept of relative benefit. While relative benefit reflects the effects of an intervention, it tends to overlook the impact of baseline risk and characteristics of the patients and may be difficult to interpret and incorporate in clinical practice. For example, a drug that decreases the frequency of an outcome [risk ratio (RR) = 0.5] will help only 1 of every 100 patients if the base rate of the outcome in the control group is 2% (decreased in the active group to 1%), but will help 20 of every 100 patients if the base rate of the outcome in the control group is 40% [6]. Therefore, to provide a more comprehensive assessment, we introduce the concept of the absolute effect indicator as a supplementary measure. The absolute benefit, which holds greater significance in public health considerations and is more relevant to group decision-making, is an indispensable evaluation metric [6].

The number needed to treat (NNT), defined as the inverse of the absolute risk difference, arguably stands as one of the most clinically intuitive indicators of treatment benefit [7–9]. It serves to communicate both statistical and clinical significance by converting a rate into a tangible frequency, thereby translating trial outcomes into practical indicators [10]. The use of the NNT could aid clinicians in making practical decisions based on patients' baseline cardiovascular disease (CVD) risk, and it can assist the judgment of medication authorities [11, 12].

Previous studies have demonstrated that cholesterol-lowering therapy reduces the risk of CVD and that the risk reduction depends on baseline values [2, 13–15]. The study was compared with previous studies. Firstly, the baseline CVD risk and the risk reduction with therapy were included in the effect values. Secondly, the trend between baseline LDL-C and CVD was shown more visually. Finally, comparing the effects of different drugs helps individual clinicians support their decisions and tell clinicians and patients how much effort is needed to achieve a particular therapeutic outcome.

NNT shows the treatment potency of the three classes of drugs in individuals with different LDL-C values, visually demonstrating the concept of gradient between LDL-C and CVD. It is essential to summarize the benefits and harms of antihyperlipidemic drugs, especially among individuals at varying CVD risk values, to inform guidelines [16, 17]. Therefore, this study aims to use the number needed to treat (NNT) in exploring the benefits and risks of antihyperlipidemic medications among individuals with different baseline LDL-C values.

## 2 Materials and Methods

### 2.1 Search Strategy and Selection Criteria

This study adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [18]. Searches were conducted up to 6 August 2023 and involved the following databases: PubMed/Medline, EMBASE, CENTRAL (Cochrane Central Register of Controlled Trials), and Web of Science. A comprehensive list of search terms, as well as the criteria for inclusion and exclusion, can be found in the Supplementary materials (Supplementary Text 1).

Primary inclusion criteria comprised the following: (1) phase 2 or 3 randomized controlled trials (RCTs) comparing antihyperlipidemic drugs to placebo, standards of care, and usual care; (2) trial follow-up duration exceeding 1 year; and (3) trials that reported primary efficacy outcomes, including myocardial infarction (MI), stroke, coronary revascularization (angioplasty or bypass grafting), cardiovascular mortality, and all-cause mortality. The major adverse cardiovascular events (MACE) encompassed cardiovascular death, MI, stroke, and coronary revascularization. Secondary outcomes encompassed cancer incidence, injection-site reaction, myalgias and myopathy, and aminotransferase elevation. Studies with fewer than 100 participants were excluded.

### 2.2 Data Extraction

Two independent investigators (HW and ZZ) systematically collected information in duplicate, using predefined data collection forms for aggregated study-level data. Discrepancies were resolved through discussion and consensus with a third reviewer (SQ) when necessary. The collected data encompassed the trial name, publication years, total and pre-arm participants numbers, medication type, participants' mean age, gender distribution, follow-up duration, baseline LDL-C, mean body mass index (BMI), and primary

and secondary endpoints for each arm. The bias risk was evaluated by the Cochrane risk of bias assessment tool (Supplementary Fig. 1).

### 2.3 Statistical Analysis

Pooled RRs and number needed to treat (NNT) were computed using a random-effects model. Fixed-effects models were also provided in the Supplementary materials. Heterogeneity was evaluated by average dispersion in effect sizes $\tau^2$, Cochran's $Q$ statistic, and Higgins and Thompsons's $I^2$, with $I^2$ values categorized as minimal (< 25%), moderate (25–50%), or substantial (> 50%). The primary model utilized random-effects meta-regression to explore LDL-C values association with cardiovascular events. For statistical hypothesis testing for meta-regression, the following were used: (1) normality of residuals using histograms, Q-Q plots, and P-P plots; (2) independence of residuals using the Durbin–Watson test, where autocorrelation is not considered to be present if it is between 1.5 and 2.5; (3) homoscedasticity plots of standardized residuals versus standardized predicted values; and (4) linearity evaluated using visual scatterplots. LDL-C values were categorized into four ranges for risk classification: < 100, 100–129, 130–159, and ≥ 160 mg/dL [5]. A two-tailed $P$-value < 0.05 was considered statistically significant.

NNT, which can represent the number needed to treat for beneficial (NNTB) outcomes and for harmful (NNTH) outcomes, was computed by the formula NNT = 1/([1 − RR] × CER), where CER represents the control event rate. NNT values were rounded up to the nearest whole number. If the NNT included infinity, it was not statistically significant. The NNT was standardized when comparing studies with varying observation periods, employing the strategy of Laupacis et al. as follows: NNT: T × T ÷ S = NNT:S, where NNT: T represents the true NNT, NNT:S represents the adjusted NNT, T represents the follow-up time, and S represents the average follow-up time [19].

The quality of the evidence was assessed according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria, which considered study design, risk of bias, inconsistency, indirectness, imprecision, and other relevant factors [20]. Sensitivity analyses were prespecified for the primary endpoint by excluding trials.

Review Manager V.5.4.1 (RevMan), GRADEpro software, R software V.4.2.1, and Stata, V.17.0 (Stata Corp.) were utilized for all analyses.

## 3 Results

### 3.1 Study Selection and Patient Population

Our literature search yielded 13,640 records in total, with contributions from various sources including Web of Science (2931 articles), the Cochrane Library (5526 articles), PubMed (702 articles), and EMBASE (4481 articles). After a rigorous selection process, 46 studies met the eligibility criteria for this meta-analysis [21–63]. These included 23 studies involving statins, 9 studies involving ezetimibe, and 14 studies involving PCSK9 inhibitors. Figure 1 provides a flowchart illustrating the study selection process. The follow-up periods in these studies varied from 1 to 6 years, with an average period of 3.0 years. Baseline LDL-C values spanned from 89 to 192 mg/dL. Supplementary Table 1 outlines the features of the studies in this analysis.

### 3.2 Major Adverse Cardiovascular Events

The risk reduction in major adverse cardiovascular events (MACE) associated with statins, ezetimibe, and PCSK9 inhibitors compared with the control group was RR 0.78 (95% CI 0.73–0.82; $P < 0.00001$), RR 0.86 (95% CI 0.78–0.94; $P = 0.002$), and RR 0.82 (95% CI 0.79–0.86; $P < 0.00001$), respectively. However, this effect exhibited variation according to baseline LDL-C values (Supplementary Fig. 2). Subgroup analysis demonstrated that the reduction in MACE risk increased with higher baseline LDL-C values (Fig. 2). Notably, the subgroup characterized by baseline LDL-C values of 130–159 mg/dL or greater achieved the most substantial reductions. In all three of the statin trial's subgroups with baseline LDL-C values greater than 100 mg/dL, statins significantly further reduced MACE compared with controls. This significance was particularly evident in trials with baseline LDL-C values of 100–129 mg/dL (NNTB 52, 95% CI NNTB 33–201; $P = 0.010$), 130–159 mg/dL (NNTB 29, 95% CI NNTB 25–35; $P < 0.00001$), and ≥ 160 mg/dL (NNTB 16, 95% CI NNTB 12–33; $P < 0.00001$). In ezetimibe trials, the reduction in MACE risk was associated with baseline LDL-C values of < 100 mg/dL (NNTB 60, 95% CI NNTB 43–120; $P < 0.0001$), 100–129 mg/dL (NNTB 31, 95% CI NNTB 21–54; $P < 0.0001$), and 130–159 mg/dL (NNTB 6, 95% CI NNTB 4–12; $P = 0.0006$). In PCSK9 inhibitor trials, a statistically significant difference was observed in trials with baseline LDL-C values of < 100 mg/dL (NNTB 29, 95% CI NNTB 21–44; $P < 0.00001$), 100–129 mg/dL (NNTB 27, 95% CI NNTB 19–57; $P = 0.0005$), and 130–159 mg/dL (NNTB 13, 95% CI NNTB 8–171; $P = 0.04$).

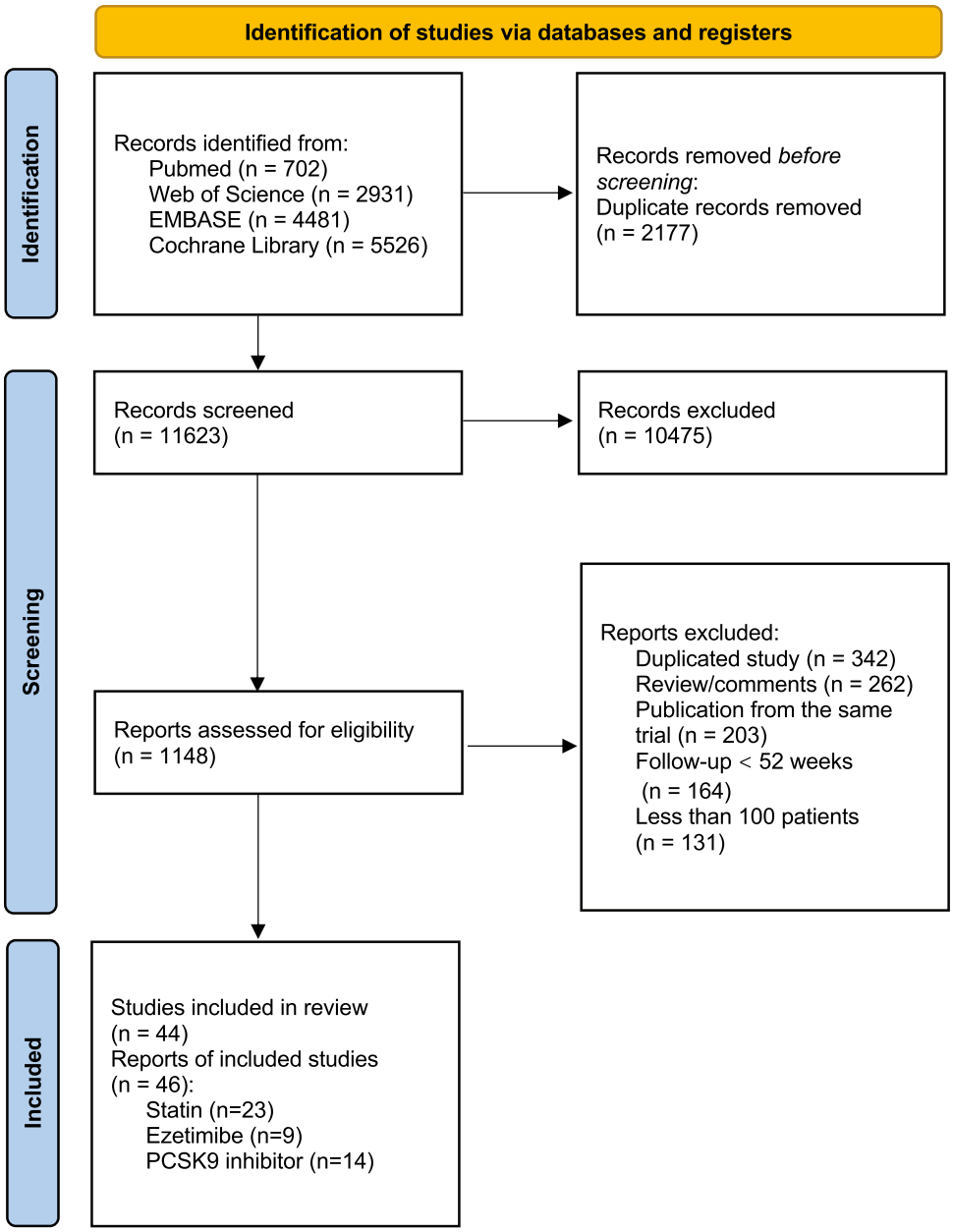


**Fig. 1** Flowchart of study selection for meta-analysis

Figure 3 graphically illustrates the impact of antihyperlipidemic medications on MACE. For the sake of comparability, the NNT was transformed to represent the number of individuals who could avoid MACE when 100 individuals received treatment for 3.0 years. Figure 4 provides a visual representation of NNT for efficacy and safety outcomes in the overall study population.

### 3.3 Myocardial Infarction

The risk reduction in myocardial infarction (MI) attributed to statin, ezetimibe, and PCSK9 inhibitor compared with control was RR 0.72 (95% CI 0.67–0.77; $P < 0.00001$), RR 0.87 (95% CI 0.80–0.93; $P = 0.0002$), and RR 0.77 (95% CI 0.67–0.88; $P < 0.0001$), respectively (Supplementary Fig. 4). In statin trials, the proportion of risk reduction for MI increased with initial LDL-C values greater than 100 mg/dL. Statistically significant differences were observed in studies with initial LDL-C values of 100–129 mg/dL (NNTB 197, 95% CI NNTB 139–382; $P = 0.0003$), 130–159 mg/dL (NNTB 77, 95% CI NNTB 65–104; $P < 0.00001$), and $\geq$ 160 mg/dL (NNTB 38, 95% CI NNTB 30–60; $P < 0.00001$; Supplementary Fig. 22). For participants with LDL-C values of 100–159 mg/dL, ezetimibe did not exhibit significant effects on MI, but statistically significant results were found for LDL-C values of < 100 mg/dL (NNTB 79, 95% CI NNTB 50–190; $P = 0.001$). In PCSK9 inhibitor trials, a significant difference was observed in trials with

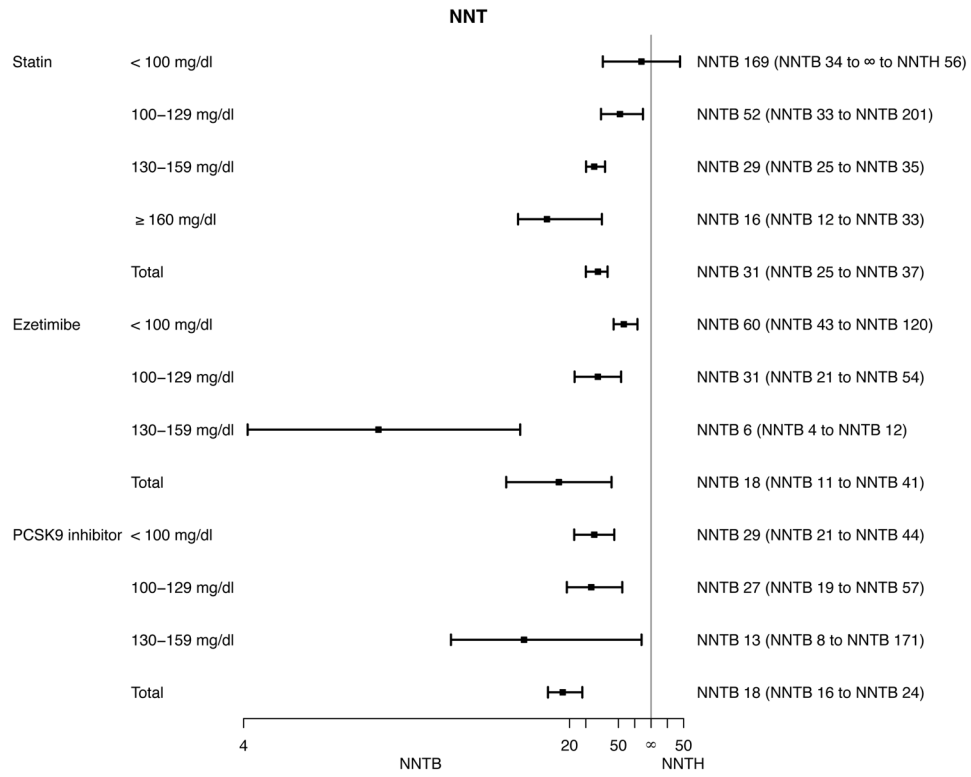


**Fig. 2** The NNTs for major adverse cardiovascular events across different baseline LDL-C. The mean follow-up duration was 3.0 years. PCSK9, proprotein convertase subtilisin/Kexin type 9; NNT, the number needed to treat; NNTB, the number needed to treat to benefit; NNTH, the number needed to treat to harm

baseline LDL-C values of < 100 mg/dL (NNTB 74, 95% CI NNTB 48–185; $P = 0.002$) and 100–129 mg/dL (NNTB 71, 95% CI NNTB 45–921; $P = 0.004$), but not for participants with LDL-C values of 130–159 mg/dL.

### 3.4 Stroke

The risk reduction in stroke associated with statin, ezetimibe, and PCSK9 inhibitor compared with control was RR 0.89 (95% CI 0.81–0.97; $P = 0.01$), RR 0.85 (95% CI 0.75–0.96; $P = 0.008$), and RR 0.78 (95% CI 0.68–0.90; $P = 0.0006$; Supplementary Fig. 6). In statin trials, the risk reduction in stroke was associated with initial LDL-C values of 130–159 mg/dL (NNTB 296, 95% CI NNTB 178–1186; $P = 0.008$) and ≥ 160 mg/dL (NNTB 280, 95% CI NNTB 161–6433; $P = 0.04$; Supplementary Fig. 23). In ezetimibe trials, the effect was associated with initial LDL-C values of 100–129 mg/dL (NNTB 107, 95% CI NNTB 67–445; $P = 0.01$). In PCSK9 inhibitors trials, a statistically significant difference was present with initial LDL-C values of < 100 mg/dL (NNTB 212, 95% CI NNTB 143–443; $P = 0.0003$).

### 3.5 Coronary Revascularization

The study investigated the risk reduction in coronary revascularization attributed to statins, ezetimibe, and PCSK9 inhibitors compared with a control group. The results were RR 0.76 (95% CI 0.71–0.81; $P < 0.00001$), RR 0.82 (95% CI 0.68–0.99; $P = 0.04$), and RR 0.81 (95% CI 0.73–0.90; $P < 0.0001$), respectively (Supplementary Fig. 8). A subgroup analysis demonstrated that the effectiveness of these interventions in reducing coronary revascularization risks was influenced by baseline LDL-C values. In statin trials, statistically significant differences were observed in patients with initial LDL-C values of 100–129 mg/dL (NNTB 222, 95% CI NNTB 143–600; $P = 0.004$), 130–159 mg/dL (NNTB 85, 95% CI NNTB 69–112; $P < 0.00001$), and ≥ 160 mg/dL (NNTB 51, 95% CI NNTB 41–68; $P < 0.00001$; Supplementary Fig. 24). In ezetimibe trials, the effect was associated with baseline LDL-C values of 100–129 mg/dL (NNTB 69, 95% CI NNTB 44–225; $P = 0.007$), and 130–159 mg/dL (NNTB 8, 95% CI NNTB 5–19; $P = 0.002$). In PCSK9 inhibitor trials, the effect was associated with initial LDL-C values of < 100 mg/dL (NNTB 64, 95% CI NNTB 44–121; $P < 0.0001$) and 130–159 mg/dL (NNTB 12, 95% CI NNTB 8–44; $P = 0.01$).

### 3.6 All-cause Mortality

The analysis of all-cause mortality risk reduction attributed to statins compared with the control group showed RR 0.90 (95% CI 0.86–0.95; $P < 0.0001$; Supplementary Fig. 10). However, this reduction was not statistically significant for ezetimibe and PCSK9 inhibitors. Statistically significant differences were observed in statin trials with initial LDL-C values of 130–159 mg/dL (NNTB 178, 95% CI NNTB


**Fig. 3** Cates plot of the NNTs for major adverse cardiovascular events (MACE) across different baseline LDL-C. Each region is the value of NNT of MACE in one LDL-C level, and the 100 faces correspond to the patients treated with antihyperlipidemic medication. A green face means patients did not experience an MACE. A yellow face means patients that would not have an MACE if treated. A red face means patients experienced an MACE even if treated

114–399; $P = 0.002$) and ≥ 160 mg/dL (NNTB 77, 95% CI NNTB 58–126; $P < 0.0001$; Supplementary Fig. 25). No significant differences in all-cause mortality were found between ezetimibe and PCSK9 inhibitors.

### 3.7 Cardiovascular Mortality

The risk reduction in cardiovascular mortality attributed to statins compared with control was RR 0.81 (95% CI 0.75–0.87; $P < 0.0001$; Supplementary Fig. 12). However, no significant effects were observed for ezetimibe and PCSK9 inhibitors. In statin trials, statistically significant differences were present in patients with baseline LDL-C values of 130–159 mg/dL (NNTB 162, 95% CI NNTB 132–224; $P < 0.00001$) and ≥ 160 mg/dL (NNTB 83, 95% CI NNTB 65–127; $P = 0.0006$; Supplementary Fig. 26). No significant differences in cardiovascular mortality were observed between ezetimibe and PCSK9 inhibitors.

### 3.8 Safety Outcomes

The incidence of cancer, myalgias, myopathy, or aminotransferase elevation did not differ significantly between patients on statins, ezetimibe, and PCSK9 inhibitors compared with the control group. However, an increased risk of injection-site reactions was attributed to PCSK9 inhibitors (RR 1.68,

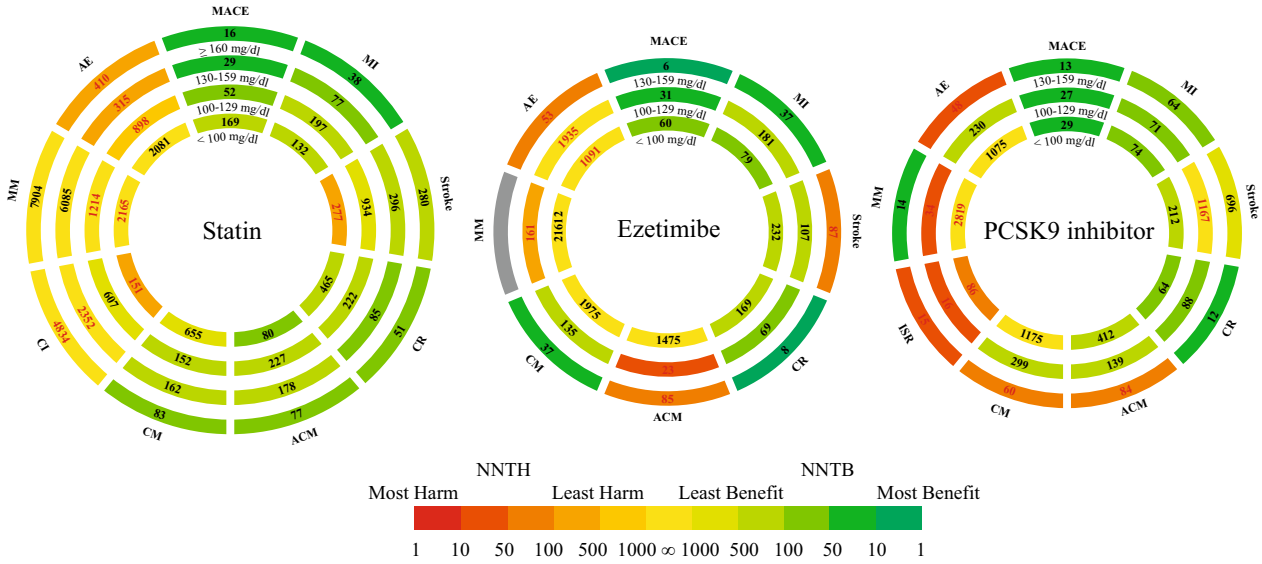


**Fig. 4** The rank-heat plot of the NNT values for all outcomes across different LDL-C values. Circles from the inside out refer to small to large baseline LDL values. The number of endpoints reported for each drug divides the circle into sectors. The NNT value for each section is labeled red if it is NNTH and black if it is NNTB. Each section is colored according to the NNT value of the corresponding LDL-C values and outcome. The scale consists of the transformation of three colors: red (NNTH = 1), yellow (NNT = ∞), and green (NNTB = 1). Gray indicates no report. *ACM* all-cause mortality, *AE* aminotransferase elevation, *CI* cancer incidence, *CM* cardiovascular mortality, *CR* coronary revascularization, *ISR* injection-site reaction, *MACE* major adverse cardiovascular events, *MI* myocardial infarction, *MM* myalgias and myopathy, *NNT* the number needed to treat, *NNTB* the number needed to treat to benefit, *NNTH* the number needed to treat to harm, *PCSK9* proprotein convertase subtilisin/Kexin type 9

95% CI 1.35–2.11; Supplementary Fig. 20). Statistically significant differences were present in individuals with initial LDL-C values of < 100 mg/dL (NNTH 86, 95% CI NNTH 229–48; $P < 0.00001$) and 100–129 mg/dL (NNTH 16, 95% CI NNTH 95–6; $P < 0.00001$; Supplementary Fig. 30).

### 3.9 Meta-Regression Analysis and Publication Bias

The residuals followed a normal distribution (Supplementary Fig. 31). The Durbin–Watson (D-W) test value was 2.075. Homoscedasticity was met (Supplementary Fig. 32). The relationship appeared linear (Supplementary Fig. 33). According to predefined baseline characteristics, the meta-regression analysis revealed no evidence of differences in the effects of antihyperlipidemic medication on MACE in mean age, year published, BMI, the percentage of male participants, diabetes mellitus, coronary artery disease, and follow-up years (Supplementary Table 11). There was statistical significance related to baseline LDL-C. We further focused on the relationship between baseline LDL-C and

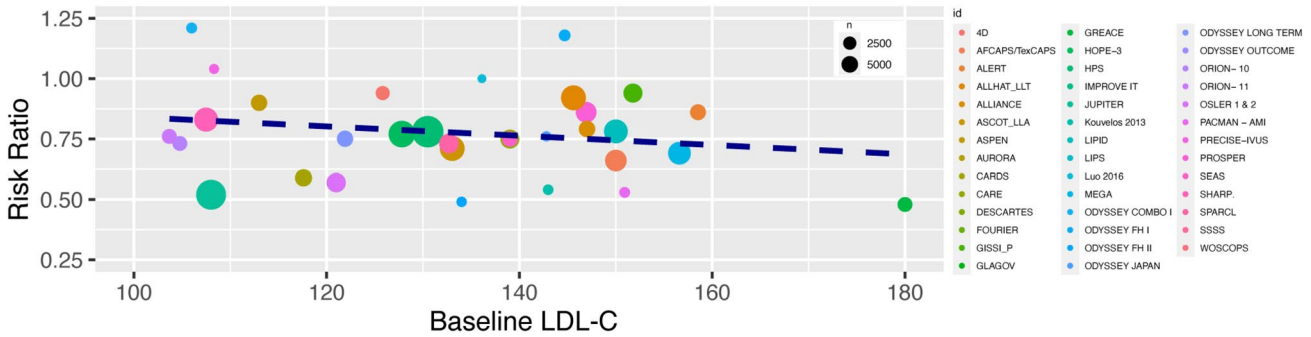


**Fig. 5** Meta-regression analysis of major adverse cardiovascular events (MACE) by baseline LDL-C level. Each color circle represents one study. The size of the circle is proportional to the number of people in the study. The dotted line represents the meta-regression slope of the change in risk ratio for treatment across increasing values of baseline LDL-C. To convert LDL-C values to mmol/L, multiply by 0.0259

intervention effect sizes (Fig. 5). In the meta-regression, baseline LDL-C values explained 13.12% of the heterogeneity, and higher baseline LDL-C values were associated with smaller RRs for MACE. We could not find any evidence of publication bias in the funnel plots, Begg's rank correlations ($P = 0.90$), and Egger's linear regression ($P = 0.056$; Supplementary Fig. 37). Sensitivity analyses were prespecified (Supplementary Fig. 38).

## 4 Discussion

The results of our meta-analyses show that higher baseline LDL-C values were associated with a greater effect of reducing MACE risks, regardless of which drug was used. CVD risk reduction that is proportional to the absolute LDL-C gradient has been demonstrated in previous studies [64]. The antihyperlipidemic medication will produce very different absolute gradients in LDL-C depending on baseline LDL-C values. This suggests that, counterintuitively, the lower the baseline LDL-C values, the higher the antihyperlipidemic therapy strength required. The latest guidelines suggest that, if baseline LDL-C is lower, the aim should not be an absolute threshold but rather to achieve 50% LDL-C reduction [3].

It is worth noting that a previous meta-analysis on antihyperlipidemic medications also reported that initial LDL-C values were related to reductions in total and cardiovascular mortality risks. It has demonstrated that more intensive, compared with less intensive, LDL-C lowering was associated with a greater reduction in risk of total and cardiovascular mortality at baseline in trials with LDL-C levels above 100 mg/dL. Such expositions are unsatisfactory because they did not fully utilize RCT evidence and overlooked variations in baseline risk [5]. Because the incidence of these events varies among patients with different baseline LDL-C values, relying solely on relative indicators may lead to either overestimating or underestimating the treatment effects.

Our analysis reveals a trend toward more substantial proportional reductions in MACE as LDL-C values increase. This trend suggests that adopting a high-risk strategy can be more cost-effective. However, if the treatment potency is taken into account, the lower the baseline LDL-C, the higher the intensity of the therapy should be to achieve a lower CVD risk reduction. The American College of Cardiology/American Heart Association (ACC/AHA) has already adjusted the threshold for initiating statin therapy from a 10-year cardiovascular risk of 20–7.5% [3]. Lowering the LDL-C threshold would further mitigate cardiovascular risk, but it would also entail more individuals receiving medication and consequently being exposed to potential adverse drug reactions. Therefore, it is imperative to thoroughly investigate the benefits and risks for populations with diverse baseline LDL-C values. Our study focuses on absolute risk reduction, considering the control event rate. NNT makes people realize that, counterintuitively, with higher initial LDL-C, it is easy to reduce the risk of CVD, while lower initial LDL-C requires a lot more treatments and a lot more treated patients to prevent one adverse cardiovascular event. Fortunately, regarding the risk of side effects, only PCSK9 inhibitors were found to cause increased injection-site reactions. Although there was no statistically significant difference in the incidence of adverse reactions between statins and ezetimibe compared with controls, results should be interpreted with caution. Our findings closely resemble those of the Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis, which reported a 15% reduction in major vascular events per 1 mmol/L reduction in LDL cholesterol with statin therapy [2]. Nevertheless, interpreting relative risk reduction can be misleading, especially in cases where some included trials achieved LDL-C reductions of less than 1 mmol/L [65]. The difficulty of lowering baseline LDL-C values by the same extent is different. The extent of LDL-C reduction depends on both the initial LDL-C values and the effectiveness of the drug [5]. Higher baseline LDL-C values correspond to higher baseline risk when LDL-C values exceed 100 mg/dL. Understanding the trends in the impact of LDL-C values on treatment efficacy and safety can inform strategies for reducing the burden of CVD and guide the development of guidelines [66].

The use of NNT as an absolute effect measure to express the consequences of clinical interventions has some potential advantages. Firstly, the RR does not reflect the magnitude of the risk without therapy [19]. The NNT conveys clinical results in a way that takes into account both the baseline risk without therapy and the risk reduction with therapy. We found that higher baseline LDL-C values were associated with higher baseline risk when baseline LDL-C values were > 100 mg/dL. However, this association was not present when the baseline LDL-C values were less than 100 mg/dL. The baseline risk of MACE was greatest for all three drugs in the subgroup with baseline LDL-C < 100 mg/dL. This trend could stem from differences in the trial population characteristics. Secondly, the NNT tells clinicians and patients how much effort is needed to achieve a particular therapeutic outcome [19]. For example, in our MACE outcomes, the subgroup with LDL-C values of 100–129 mg/dL (RR 0.77) treated with statins had lower RR values than the subgroup with LDL-C values of 130–159 mg/dL (RR 0.79). Normally we would assume that the two subgroups with similar efficacy and lower RR values would be better. However, the NNT values tell us that the subgroup with LDL-C 130–159 mg/dL would need 29 treated patients to prevent one MACE, whereas the subgroup with 100–129 mg/dL need 52 treated patients. Not only was there a significant difference in efficacy between

the two subgroups, but also the LDL-C 130–159 mg/dL group had better efficacy. Finally, the NNT allowed us to compare the consequences of different interventions. Most of the research on antihyperlipidemic drugs has been limited to comparing the same type of drugs. However, our study calculated the NNT of different types of antihyperlipidemic drugs, visually demonstrating the concept of gradient between LDL-C and CVD.

Our study focuses on the association between the efficacy and safety of the three anti-hyperlipidemic drugs and baseline LDL-C values. The NNT adequately demonstrates the efficacy of various lipid-lowering drugs in different LDL-C settings and very intuitively shows the relationship between LDL-C and cardiovascular disease risk. We applied the GRADE framework to evaluate the quality of the studies, thereby substantiating the validity of our meta-analysis results. The clinical significance of our study is that it aids physicians and patients in understanding how much effort is required to prevent a particular outcome. Furthermore, it is worth discussing how many people to treat and whether how long it takes to prevent a single cardiovascular disease event is acceptable, which is a crucial aspect of clinical decision-making. Our study calculates NNT values to guide clinical decisions on the prescription of antihyperlipidemic drugs, providing clinicians, health economists, and policymakers with reliable, critically assessed, and precise estimates of treatment effects and safety.

Nonetheless, our meta-analysis does have several limitations. Firstly, there was a degree of heterogeneity among the included studies, possibly due to variations in the definitions of major cardiovascular composite endpoints, despite our attempts to standardize them. Secondly, the trials varied in duration, with ezetimibe and PCSK9 inhibitors having shorter mean follow-up times compared with statins, which could affect comparability. Third, our analysis was based on study-level data. To address these limitations, future studies should aim to include more trials with individual data and a specific focus on LDL-C values.

## 5 Conclusion

In conclusion, our study utilizes the concept of NNT to show the treatment potency of statins, ezetimibe, and PCSK9 inhibitors of drugs in individuals with different LDL-C values, visually demonstrating the concept of gradient between initial LDL-C and CVD risk. In addition, both statins and ezetimibe demonstrate a favorable safety profile, and PCSK9 inhibitors warrant attention on injection-site reactions. The concept of NNT serves as a valuable tool for quantifying the magnitude of benefits and risks, offering indispensable guidance for patients with hyperlipidemia.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s40256-024-00651-7.

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## Declarations

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**Conflict of Interest** H-FW, Y-CM, S-FQ, X-YX, Z-YZ, CG, KS, and Q-BT declare that they have no potential conflicts of interest that might be relevant to the contents of this manuscript.

**Authors' Contributions** H-FW conceived the report and wrote the initial manuscript drafting. Y-CM and ZYZ participated in the investigation process. X-YX and S-FQ provided support for formal analysis and contributed to manuscript writing, review, and editing. Q-BT played a vital role in the project, overseeing it, contributing to the conceptualization, and developing the methodology. All collaborators contributed to the final article.

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