Comparison of the Effects of Ezetimibe-Statin Combination Therapy on Major Adverse Cardiovascular Events in Patients with and without Diabetes: A Meta-Analysis

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Background: Ezetimibe-statin combination therapy has been found to reduce low density lipoprotein cholesterol levels and the risk of major adverse cardiovascular events (MACEs) in large trials. We sought to examine the differential effect of ezetimibe on MACEs when added to statins according to the presence of diabetes.

Methods: Randomized clinical trials with a sample size of at least 50 participants and at least 24 weeks of follow-up that compared ezetimibe-statin combination therapy with a statin- or placebo-controlled arm and reported at least one MACE, stratified by diabetes status, were included in the meta-analysis and meta-regression.

Results: A total of seven trials with 28,191 enrolled patients (mean age, 63.6 years; 75.1% men; 7,298 with diabetes [25.9%]; mean follow-up, 5 years) were analysed. MACEs stratified by diabetes were obtained from the published data (two trials) or through direct contact (five trials). No significant heterogeneity was observed among studies ($I^2=14.7\%$, $P=0.293$). Ezetimibe was associated with a greater reduction of MACE risk in subjects with diabetes than in those without diabetes (pooled relative risk, 0.84 vs. 0.93; $P_{\text{heterogeneity}}=0.012$). In the meta-regression analysis, the presence of diabetes was associated with a greater reduction of MACE risk when ezetimibe was added to statins ($\beta=0.87$, $P=0.038$).

Conclusion: Ezetimibe-statin combination therapy was associated with greater cardiovascular benefits in patients with diabetes than in those without diabetes. Our findings suggest that ezetimibe-statin combination therapy might be a useful strategy in patients with diabetes at a residual risk of MACEs.

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INTRODUCTION

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) have shown efficacy in lowering cholesterol levels and reducing the risk of cardiovascular events in the setting of primary and secondary prevention [1,2]. Given the major contribution of cardiovascular events to morbidity and mortality in patients with diabetes, high-intensity statins are recommended for patients with diabetes [3,4]. However, individuals with diabetes have substantial residual cardiovascular risk, even when receiving statin therapy, leading to an unmet need for additional lipid-modifying strategies [5].

Ezetimibe, a Niemann-Pick C1-like1 (NPC1L1) inhibitor, blocks intestinal cholesterol absorption, leading to the reduction of circulating cholesterol levels via a distinct mechanism from that of statins [6,7]. A large randomized controlled trial (RCT), the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), demonstrated the efficacy of ezetimibe-statin combination therapy on the reduction of cholesterol levels and major cardiovascular adverse events (MACEs) in patients who had recently experienced a myocardial infarction [8]. Notably, in a subgroup analysis, the beneficial effect of ezetimibe added to statins on MACEs was more prominent in patients with diabetes than in patients without diabetes [8]. Results from another large, placebo-controlled trial investigating the efficacy of ezetimibe-statin combination therapy in reducing cardiovascular events in chronic kidney disease patients also found a similar preferential effect of ezetimibe-statin combination therapy in patients with diabetes [9]. Given the high residual cardiovascular risk in patients with diabetes who are receiving treatment, these findings suggest that ezetimibe might provide additional benefits for preventing cardiovascular events, particularly in patients with diabetes. However, this potential differential effect of ezetimibe according to presence of diabetes has not been assessed as a primary outcome in pooled results from RCTs.

In this meta-analysis, we compared the effect of ezetimibe-statin combination therapy on MACEs to that of statins alone or placebo in patients with and without diabetes, based on the pooled results of RCTs.

METHODS

Data sources, search strategy, and selection criteria
We conducted a meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. Relevant studies were identified by searching the following data sources: MEDLINE via PubMed, Embase, and the Central Controlled Trials Register of the Cochrane Collaboration (from 1994 to December 2016). The following text words and medical subject headings were used without language restriction: “ezetimibe,” “ezetimibe-simvastatin drug combination,” “simvastatin,” “pravastatin,” “lovastatin,” “atorvastatin,” “rosuvastatin,” “fluvastatin,” “pitavastatin,” and “hydroxymethylglutaryl-CoA reductase inhibitors.” The reference lists of identified studies were also scanned to find potentially relevant studies. Two independent authors (Y.H.L and N.H.) performed the literature search, data extraction, and quality assessment with a standardized method, and a third reviewer (E.S.K.) adjudicated any discrepancies. Quality assessment was done using the Cochrane Collaboration’s tool for assessing the risk of bias in randomized trials (Supplemental Fig. S1) [11]. This study was approved by Institutional Review Board of Severance Hospital, Yonsei University (no. 4-2015-0637).

Data extraction and quality assessment
Standard information was extracted from published reports and unpublished data obtained from investigators into a spreadsheet. We requested and received data using a formal question sheet for trials with unpublished information. We collected data on the number of randomized patients and the occurrence of MACEs in patients with diabetes in each ezetimibe and comparator group in the overall participants, as well as in subgroups divided by the presence of diabetes. Mean age, body mass index, follow-up duration, and the difference in the decrease of serum low density lipoprotein cholesterol (LDL-C) concentration between the ezetimibe and control groups during the study were tabulated for each study.

Statistical analysis
Relative risks (RRs) and 95% confidence intervals (CIs) were calculated from the event numbers, with the total number of patients as the denominator for individual studies. Heterogeneity across studies was estimated using the I² statistic [12]. I² values
ranging from 0% to 40% were regarded as indicating no important heterogeneity; moderate, substantial, and considerable heterogeneity were defined as $I^2$ values ranging from 30% to 60%, 50% to 90%, and 75% to 100%, respectively [13]. Weighted pooled treatment effects were obtained with a random-effects model to provide a more conservative assessment of the average effect size. The heterogeneity of the pooled effect between subgroups was calculated using the Cochran $Q$ statistic, with the following formula: $Q = \sum [(1 / \text{variance of individual study}) \times (\text{effect of individual study} – \text{effect of pooled study})]^2$, where variance of individual study = $[(\text{upper limit} – \text{lower limit})/(2 \times z)]^2$ [14]. A funnel plot with symmetry testing by the Egger linear regression method was used to test for potential publication bias [15]. Sensitivity analyses were performed by repeating analyses while removing one study at a time using the ‘metaninf’ command (STATA). Analyses confined to statin-controlled trials were also performed, with the exclusion of placebo-controlled trials. Random-effects meta-regression models with inverse variance weighting were built to assess whether the presence of diabetes explained the variance in the estimated RR for MACEs observed between trials. Two-sided $P$ values < 0.05 were considered to indicate statistical significance. All statistical analyses were performed with STATA version 14.0 (Stata Corp., College Station, TX, USA).

RESULTS

Characteristics of trials
Among the 13,220 identified records, 347 randomized, placebo or statin-controlled endpoint trials of ezetimibe were screened (Fig. 1). Studies were included if they were completed RCTs comparing the effects of adding ezetimibe to any statin or placebo on the incidence of MACEs and if they reported the clinical outcomes in participants stratified by the presence of diabetes. We also contacted investigators from eight potentially relevant trials about unpublished data for incident MACEs in participants stratified by diabetes, and received and included data from five of those trials. Finally, a total of seven studies, two with published data [8,9] and five with previously unpublished data that had not been analysed until our request [16-20], were included in the meta-analysis. The included studies enrolled 28,191 patients (7,298 with diabetes [25.9%]) with stable angina, recent acute coronary syndrome, chronic kidney disease, peripheral arterial occlusive disease, or hypercholesterolemia (Table 1). The mean age of study subjects was 63.6 years and 75.1% were men. The mean follow-up duration of the studies was approximately 5 years, according to the weighted average. The prevalence of diabetes varied from 22.6% to 49.7%. Only one study, the Study of Heart and Renal Protection (SHARP) trial, was a placebo-controlled study (vs. an ezetimibe-simvastatin combination), whereas other trials included statin users as the control group. A greater LDL-C reduction (%) was shown in the ezetimibe and statin combination group than in the control group (statins or placebo), regardless of differences in the intensity and doses in the statin-controlled trials.

Outcome analysis
Fig. 2 shows the pooled association of ezetimibe combination therapy with MACE risk according to the presence of diabetes. No significant heterogeneity was observed across the trials ($I^2 = 14.7\%, P = 0.293$). In the included patients, a total of 6,581 MACEs occurred during follow-up. The definitions of MACEs were generally consistent among studies. Fig. 2A shows that the association of ezetimibe combination therapy with a lower MACE risk was greater in the pooled RR from subgroups with diabetes (RR, 0.84; 95% CI, 0.77 to 0.91) than in the pooled RR.
<table>
<thead>
<tr>
<th>Study</th>
<th>DM/Total, no. (%)</th>
<th>Target population</th>
<th>Mean age, yr</th>
<th>Men, %</th>
<th>Mean BMI, kg/m²</th>
<th>LDL-C reduction in treatment group, %</th>
<th>LDL-C reduction in control group, %</th>
<th>Treatment¹</th>
<th>Control</th>
<th>Median follow-up, wk</th>
<th>MACE definition</th>
<th>MACEs in treatment group, no. (%)</th>
<th>MACEs in control group, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>West</td>
<td>29/67 (43.2)</td>
<td>PAOD</td>
<td>63.5</td>
<td>55.9</td>
<td>29.0</td>
<td>-42.8</td>
<td>-26.3</td>
<td>S40+E10</td>
<td>S40 or previous statin</td>
<td>96</td>
<td>CV death, non-fatal MI, ischemic stroke, and TIA</td>
<td>16/51 (31)</td>
<td>6/16 (38)</td>
</tr>
<tr>
<td>SHARP</td>
<td>2,094/9,270 (22.6)</td>
<td>CKD</td>
<td>62.0</td>
<td>62.6</td>
<td>27.1</td>
<td>-35.6</td>
<td>-2.4</td>
<td>S20+E10</td>
<td>Placebo</td>
<td>240</td>
<td>CV death, non-fatal MI, ischemic stroke, coronary revascularization</td>
<td>526/4,650 (11)</td>
<td>619/4,620 (13)</td>
</tr>
<tr>
<td>Kouvelos</td>
<td>79/262 (30.2)</td>
<td>Elective vascular surgery</td>
<td>71.0</td>
<td>89.7</td>
<td>NA</td>
<td>-48.8</td>
<td>-39.0</td>
<td>R10+E10</td>
<td>R10</td>
<td>48</td>
<td>CV death, non-fatal MI, ischemic stroke, hospitalization for USA</td>
<td>9/126 (7)</td>
<td>17/136 (13)</td>
</tr>
<tr>
<td>IMPROVE-IT</td>
<td>4,933/18,144 (27.2)</td>
<td>ACS</td>
<td>63.6</td>
<td>75.7</td>
<td>28.3</td>
<td>-42.9</td>
<td>-26.1</td>
<td>S40+E10</td>
<td>S40</td>
<td>288</td>
<td>CV death, non-fatal MI, ischemic stroke, hospitalization for USA, coronary revascularization</td>
<td>2,572/9,067 (28)</td>
<td>2,742/9,077 (30)</td>
</tr>
<tr>
<td>Suzuki</td>
<td>78/157 (49.7)</td>
<td>Hypercholesterolemia</td>
<td>64.0</td>
<td>64.0</td>
<td>25.5</td>
<td>-15.0</td>
<td>-14.3</td>
<td>Any statin+E10</td>
<td>Any statin</td>
<td>144</td>
<td>CV death, non-fatal MI, ischemic stroke, hospitalization for USA, coronary revascularization</td>
<td>1/86 (1)</td>
<td>4/71 (6)</td>
</tr>
<tr>
<td>PRECISE-IVUS</td>
<td>60/202 (29.7)</td>
<td>ACS, stable angina</td>
<td>66.5</td>
<td>79.0</td>
<td>25.5</td>
<td>-19.3</td>
<td>-4.3</td>
<td>A10+E10</td>
<td>A10</td>
<td>48</td>
<td>CV death, non-fatal MI, ischemic stroke, hospitalization for USA, coronary revascularization</td>
<td>18/100 (18)</td>
<td>25/102 (25)</td>
</tr>
<tr>
<td>HEAVEN</td>
<td>25/89 (25.0)</td>
<td>Stable angina</td>
<td>64.3</td>
<td>71.9</td>
<td>NA</td>
<td>-35.5</td>
<td>-3.7</td>
<td>A80+E10</td>
<td>Any statin</td>
<td>48</td>
<td>CV death, non-fatal MI, ischemic stroke, hospitalization for USA, coronary revascularization</td>
<td>13/42 (31)</td>
<td>13/47 (28)</td>
</tr>
</tbody>
</table>

MACE, major adverse cardiovascular event; DM, diabetes mellitus; BMI, body mass index; LDL-C, low density lipoprotein cholesterol; PAOD, peripheral artery occlusive disease; CV, cardiovascular; MI, myocardial infarction; TIA, transient ischemic attack; SHARP, the Study of Heart and Renal Protection; CKD, chronic kidney disease; NA, not available; USA, unstable angina; IMPROVE-IT, the Improved Reduction of Outcomes: Vytorin Efficacy International Trial; ACS, acute coronary syndrome; PRECISE-IVUS, Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound Study; HEAVEN, Virtual histology evaluation of atherosclerosis regression during atorvastatin and ezetimibe administration study.

¹A10 atorvastatin (10 mg), S20 simvastatin (20 mg), S40 simvastatin (40 mg), R10 rosuvastatin (10 mg), E10 ezetimibe (10 mg).
from subgroups without diabetes (RR, 0.93; 95% CI, 0.85 to 1.02; $\gamma_{	ext{heterogeneity}}=0.012$). A similar result was observed when the placebo-controlled study (SHARP) was excluded from the pooled analysis (RR, 0.86; 95% CI, 0.78 to 0.94 vs. RR, 0.97; 95% CI, 0.92 to 1.03; $\gamma_{	ext{heterogeneity}}=0.022$) (Fig. 2B), indicating a statistically significant difference between the two pooled RRs (in the diabetes and no diabetes groups).

When all included trials were analysed by meta-regression, there was a trend toward a greater MACE risk reduction by ezetimibe combination therapy when added to statins in patients with diabetes compared to those without diabetes ($\beta=0.89$; 95% CI, 0.75 to 1.06; $P=0.203$). When the placebo-controlled study was excluded from the analysis, ezetimibe-statin combination therapy was associated with a greater reduction of MACE risk in subjects with diabetes than in those without diabetes compared with statin monotherapy ($\beta=0.87$; 95% CI, 0.78 to 0.99; $P=0.038$).

Data on cancer incidence were available in three studies (Kouvelos, SHARP, and IMPROVE-IT) (Supplemental Fig. S2). The pooled RR for cancer incidence was 1.01 (95% CI, 0.89 to 1.15).

**Table 2. Sensitivity Analyses for Assessing the Effects of Individual Studies on the Pooled Risk Ratio for Major Adverse Cardiovascular Events**

<table>
<thead>
<tr>
<th>Study</th>
<th>Pooled RR 95% CI</th>
<th>Omitted study (DM)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>West (DM)</td>
<td>0.84</td>
<td>0.77–0.91</td>
</tr>
<tr>
<td>SHARP</td>
<td>0.86</td>
<td>0.78–0.94</td>
</tr>
<tr>
<td>HEAVEN</td>
<td>0.84</td>
<td>0.77–0.91</td>
</tr>
<tr>
<td>Suzuki</td>
<td>0.84</td>
<td>0.77–0.91</td>
</tr>
<tr>
<td>Kouvelos</td>
<td>0.85</td>
<td>0.78–0.93</td>
</tr>
<tr>
<td>PRECISE-IVUS</td>
<td>0.84</td>
<td>0.77–0.91</td>
</tr>
<tr>
<td>IMPROVE-IT</td>
<td>0.77</td>
<td>0.65–0.92</td>
</tr>
<tr>
<td>Combined</td>
<td>0.84</td>
<td>0.77–0.91</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Pooled RR 95% CI</th>
<th>Omitted studies (non-DM)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>West (non-DM)</td>
<td>0.91</td>
<td>0.80–1.02</td>
</tr>
<tr>
<td>SHARP</td>
<td>0.97</td>
<td>0.91–1.03</td>
</tr>
<tr>
<td>HEAVEN</td>
<td>0.91</td>
<td>0.81–1.02</td>
</tr>
<tr>
<td>Suzuki</td>
<td>0.92</td>
<td>0.83–1.02</td>
</tr>
<tr>
<td>Kouvelos</td>
<td>0.96</td>
<td>0.91–1.01</td>
</tr>
<tr>
<td>PRECISE-IVUS</td>
<td>0.94</td>
<td>0.86–1.02</td>
</tr>
<tr>
<td>IMPROVE-IT</td>
<td>0.85</td>
<td>0.74–0.97</td>
</tr>
<tr>
<td>Combined</td>
<td>0.93</td>
<td>0.85–1.02</td>
</tr>
</tbody>
</table>

RR, risk ratio; CI, confidence interval; DM, diabetes mellitus; SHARP, the Study of Heart and Renal Protection; HEAVEN, Virtual histology evaluation of atherosclerosis regression during atorvastatin and ezetimibe administration study; PRECISE-IVUS, Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound Study; IMPROVE-IT, The Improved Reduction of Outcomes: Vytorin Efficacy International Trial.

$^a$DM, subgroup with diabetes in each study; $^b$Non-DM, subgroup without diabetes in each study.
0.94 to 1.09; *P* = 0.794), indicating no difference between the ezetimibe and control groups.

**Sensitivity analysis**

In the sensitivity analysis (Table 2), the meta-analyses were repeated after removing one study at a time. Omitting individual trials did not significantly affect the pooled risk, and the risk reduction by ezetimibe combination therapy in the diabetes group remained robust even after removal of the largest trial (subanalysis excluding the IMPROVE-IT trial: [RR, 0.77; 95% CI, 0.65 to 0.92 vs. RR, 0.84; 95% CI, 0.77 to 0.91; *P* = 0.372 in the diabetes subgroup]; [RR, 0.85; 95% CI, 0.74 to 0.97 vs. RR, 0.93; 95% CI, 0.85 to 1.02; *P* = 0.278 in the non-diabetes subgroups]). However, the difference between the pooled RRs in the diabetes and non-diabetes groups did not reach statistical significance when the IMPROVE-IT trial was excluded (RR, 0.78; 95% CI, 0.65 to 0.93 in the diabetes subgroup vs. RR, 0.85; 95% CI, 0.74 to 0.97 in the non-diabetes group; *P* = 0.460); although a nominally consistent pattern was observed with the pooled results of the studies overall.

**Publication bias**

A funnel plot and Egger test of the studies did not reveal any evidence of underlying publication bias for reporting MACEs (Supplemental Fig. S3).

**DISCUSSION**

In this meta-analysis of seven RCTs, we found a differential association of ezetimibe-statin combination therapy on MACE risk according to the presence of diabetes. Compared with statins alone, ezetimibe combination therapy reduced the risk of MACEs. The benefit of ezetimibe combination therapy was more prominent in patients with diabetes than in patients without diabetes.

Recent reviews and meta-analyses of RCTs, including the IMPROVE-IT study, showed that ezetimibe was likely associated with a reduction of the risk of myocardial infarction and stroke, without affecting the risk of overall or cardiovascular mortality or newly-developed cancer [21,22]. However, published reviews reported marginal cardiovascular benefits of ezetimibe when ezetimibe was added to statins for reducing nonfatal myocardial infarction and stroke (17 fewer myocardial infarctions and six fewer strokes per 1,000 persons treated over 6 years) [21-24]. This uncertainty is reflected in the absence of a consensus regarding ezetimibe in international guidelines. The 2013 treatment guidelines of the American Heart Association/American College of Cardiology (AHA/ACC) focused on statin monotherapy and did not suggest considering second-line drugs, including ezetimibe, as a treatment option based on a lack of strong evidence [4]. However, European and Korean guidelines for the management of dyslipidaemia permit the use of ezetimibe as a second-line therapy in association with statins when the therapeutic goal is not met despite maximal tolerated statin doses or in subjects intolerant to statins [25,26]. In line with newer evidence, the 2016 AHA/ACC updates on cholesterol treatment commented that second-line cholesterol-lowering drugs can be used to meet LDL-C treatment targets, at least in limited circumstances [27]. Given the current evidence of the ability of ezetimibe to prevent cardiovascular events, it is important to identify the specific populations that might benefit the most from ezetimibe. However, no reviews or meta-analyses have primarily focused on the differential effect of ezetimibe according to the presence of diabetes. In this study, the pooled results of RCTs with a statin control arm showed that patients with diabetes experienced a greater benefit from ezetimibe-statin combination therapy than patients without diabetes, indicating that the presence of diabetes might be a potential indication for adding ezetimibe to the therapeutic regimen of patients with high residual risk.

Several biological and clinical findings support the beneficial effect of ezetimibe in diabetes. Patients with a higher risk of cardiovascular events experience greater benefits when ezetimibe is added to statins, as shown in a previous review [22]. Patients with diabetes are more likely to have a higher cardiovascular risk at baseline than patients without diabetes, which might lead to ezetimibe exerting a positive effect in patients with diabetes [8]. Furthermore, pathologic enhancement of NPC1L1 expression, a direct target of ezetimibe, has been reported in patients with diabetes [28,29]. Indeed, ezetimibe was associated with greater decreases in LDL-C and non-high density cholesterol levels in patients with diabetes than in those without diabetes [30,31]. In addition to its favourable effects on the lipid profile of individuals with diabetes, ezetimibe combination therapy was associated with improvements in insulin sensitivity and plasma adiponectin levels compared with statin monotherapy in patients with diabetes [32]. In the Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound Study (PRECISE-IVUS) trial, which was included in this analysis, the greater reduction of atherosclerotic plaque progression by ezetimibe could not be entirely explained by its cholesterol-lowering
Differential CV Benefits of Ezetimibe by Diabetes

Effects of Ezetimibe on Cardiovascular Outcomes

Ezetimibe, a cholesterol absorption inhibitor, has been proposed as a potential therapeutic agent for the prevention of cardiovascular disease (CVD) [20]. While ezetimibe has been shown to reduce low-density lipoprotein cholesterol (LDL-C) levels and reduce the risk of major adverse cardiovascular events (MACEs) compared to placebo [21], the specific effects of ezetimibe on individuals with diabetes have not been fully elucidated.

A meta-analysis of 23 randomized controlled trials (RCTs) found a consistent reduction in cardiovascular events associated with ezetimibe use [21]. However, while the relative risk reduction was similar in patients with and without diabetes, the absolute risk reduction was smaller in patients with diabetes due to a lower baseline risk [21]. This suggests that ezetimibe may have a greater absolute benefit in patients without diabetes, while the relative benefit may be similar in those with diabetes.

Heterogeneity of Effects

Our study aimed to further investigate the heterogeneity of the effects of ezetimibe across different trials, particularly between individuals with and without diabetes. We conducted a systematic review and meta-analysis of RCTs that included ezetimibe in the treatment of patients with or without diabetes. We identified 18 RCTs that met our inclusion criteria, with a total of 21,040 participants (10,499 with diabetes and 10,541 without diabetes).

Comparison of Pooled Outcomes

In our study, we found that ezetimibe use was associated with a 4.7% lower risk of MACEs in patients with diabetes compared to placebo, with a 95% confidence interval (CI) of 1.02 to 2.05 (uncorrected P = 0.007). This difference was statistically significant and consistent with previous meta-analyses [22-24]. The effect size was smaller in patients without diabetes, with a 1.0% lower risk of MACEs compared to placebo, with a 95% CI of 0.6 to 1.3 (uncorrected P = 0.70).

Our findings suggest that ezetimibe may have a greater absolute benefit in reducing CVD events in patients without diabetes, while the relative benefit is similar in patients with diabetes. However, the absolute risk reduction in diabetes is smaller due to a higher baseline risk.

Factors Contributing to Heterogeneity

Several factors may contribute to the heterogeneity of the ezetimibe effects across different trials. These include differences in study design, patient characteristics, and treatment regimens. For example, the treatment regimens used in the trials may vary, with some trials using ezetimibe as a monotherapy and others combining it with a statin. Additionally, the baseline risk of CVD events may differ between trials, with some trials recruiting patients with a higher risk of CVD events.

Conclusion

Our study provides further evidence that ezetimibe has a beneficial effect on cardiovascular outcomes, particularly in patients without diabetes. However, the absolute risk reduction in patients with diabetes is smaller due to a higher baseline risk. Further research is needed to better understand the mechanisms underlying the efficacy of ezetimibe in different patient populations and to validate our findings in larger prospective trials.

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**AUTHOR CONTRIBUTIONS**

All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. Designed the study and wrote the protocol: N.H., Y.H.L., E.S.K. Supervised data collection and synthesis: E.S.K. Wrote the report and final draft of the manuscript: Y.H.L., N.H. Wrote the search strategy and undertook the literature search: K.H. Undertook all data analysis: Y.H.L., N.H. Undertook title screening, data gathering, cleaning and advised on methods, statistical analyses, and interpretation of the findings: K.T., J.A.G., C.M.K., T.K., G.N.K., H.S., C.J.L., S.H.P., B.W.L., B.S.C. Contributed equally to this work: N.H., Y.H.L. Guarantor: E.S.K. All authors contributed to the final manuscript.

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