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A Bayesian network meta-analysis of PCSK9 inhibitors, statins and ezetimibe with or without statins for cardiovascular outcomes

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Abstract

Background: The comparative effects of statins, ezetimibe with or without statins and proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors remain unassessed.

Design: Bayesian network meta-analysis was conducted to compare treatment groups.

Methods: Thirty-nine randomized controlled trials were selected using MEDLINE, EMBASE, and CENTRAL (inception – September 2017).

Results: In network meta-analysis of 189,116 patients, PCSK9 inhibitors were ranked as the best treatment for prevention of major adverse cardiovascular events (Surface Under Cumulative Ranking Curve (SUCRA), 85%), myocardial infarction (SUCRA, 84%) and stroke (SUCRA, 80%). PCSK9 inhibitors reduced the risk of major adverse cardiovascular events compared with ezetimibe + statin (odds ratio (OR): 0.72; 95% credible interval (CrI), 0.55–0.95; Grading of Recommendation Assessment, Development and Evaluation (GRADE) criteria: moderate), statin (OR: 0.78; 95% CrI: 0.62–0.97; GRADE: moderate) and placebo (OR: 0.63; 95% CrI: 0.49–0.79; GRADE: high). The PCSK9 inhibitors were consistently superior to groups for major adverse cardiovascular event reduction in secondary prevention trials (SUCRA, 95%). Statins had the highest probability of having lowest rates of all-cause mortality (SUCRA, 82%) and cardiovascular mortality (SUCRA, 84%). Compared with placebo, statins reduced the risk of all-cause mortality (OR: 0.88; 95% CrI: 0.83–0.94; GRADE: moderate) and cardiovascular mortality (OR: 0.84; 95% CrI: 0.77–0.90; GRADE: high). For cardiovascular mortality, PCSK9 inhibitors were ranked as the second best treatment (SUCRA, 78%) followed by ezetimibe + statin (SUCRA, 50%).

Conclusion: PCSK9 inhibitors were ranked as the most effective treatment for reducing major adverse cardiovascular events, myocardial infarction and stroke, without having major safety concerns. Statins were ranked as the most effective therapy for reducing mortality.

Keywords

Proprotein convertase subtilisin-kexin type 9 inhibitors, statins, ezetimibe, cardiovascular events

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Introduction

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality worldwide.[1] Statins, ezetimibe and proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors have been proven to be beneficial in reducing CVD risk by decreasing low-density lipoprotein cholesterol (LDL-C). Statins are historically known to reduce CVD risk by ~25% for every

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1 mmol/L reduction in LDL-C.[2] The addition of ezetimibe to statin therapy can result in additional LDL-C reduction accompanied by exponential cardiovascular risk reduction.[3] Similarly, PCSK9 inhibitors have shown to generate incremental reductions in LDL-C compared with ezetimibe or placebo.[4,5] However, former reports have shown that major adverse cardiovascular event (MACE) reduction was considerably lower than expected in response to profound reductions in LDL-C by PCSK9 inhibitors.[4,6] This lack of linear correlation between LDL-C reduction and MACE reduction may have occurred due to small study effects in meta-analyses or inadequate duration of follow-up of the studies. We hypothesized that drugs which demonstrate more robust LDL-C reduction should also result in more robust reduction in MACEs. To test this hypothesis we performed a Bayesian network meta-analysis (NMA) comparing statins, ezetimibe with or without statins, and PCSK9 inhibitors.

Methods

This NMA is performed according to the Cochrane Collaboration guidelines[7] and is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension (PRISMA) statement for systematic reviews incorporating network meta-analyses for health care interventions.[8,9]

Data sources and searches

Data search was carried out by two authors (HR and FN) using PubMed/MEDLINE, EMBASE and CENTRAL (Cochrane Central Register of Controlled Trials) (inception – September 2017). We also reviewed clinical trial registries (www.clinicaltrials.gov, www.clinicaltrialsregister.eu), scientific meetings proceedings and references of the relevant articles. The search was restricted to English language, full text articles, human subjects and randomized controlled trials (RCTs). The following key words and MesH terms were used in combination: ''proprotein convertase subtilisin-kexin type 9'', ''proprotein convertases'', ''PCSK9'', ''alirocumab'', ''evolucumab'', ''AMG145'', ''REGN727'', ''sar236553'', ''ezetimibe'', ''hydroxymethylglutaryl-coa reductase inhibitors'', ''statin'', ''atorvastatin'', ''rosuvastatin'', ''simvastatin'', ''lovastatin'', ''fluvastatin'', ''hypercholesteremia'', ''atherosclerotic cardiovascular disease'', ''randomized controlled trials'', ''clinical trial'', ''intervention study'', ''randomized controlled trial'' and ''humans''. All the citations were downloaded to Endnote (Thompson ISI ResearchSoft, Philadelphia, Pennsylvania, USA) and duplicates were identified and removed through EndNote and manually.

Study selection

We included RCTs only, which had compared PCSK9 inhibitors, ezetimibe, statins, placebo or combinations of these in subjects with hypercholesteremia. Included studies had to report at least one clinical event among outcomes of interest in an adult population (age $\geq$ 18 years). To avoid small study effects and generate more robust evidence, we selected studies enrolling at least 100 patients and with follow-up duration $\geq$ 6 months. There were no restrictions on comorbidities. Only drugs and doses as available in European Union and United States markets were considered. Two authors (HR and ST) independently reviewed the titles and abstracts of the studies, followed by full text screening to identify the studies that met a priori inclusion criteria. The entire process was supervised by a third author (SUK) and any disagreements were resolved by mutual consensus.

Data extraction and quality assessment

Data extraction was performed independently by two authors (ST and FN) using a pre-specified collection form incorporating baseline characteristics of the participants, number of events, sample size, crude point estimates and follow-up duration. When reported, outcomes were extracted based on intention to treat principle. Whenever possible, adjusted outcomes were extracted. When available, additional information was acquired from study protocols and appendices. The discrepancies were resolved by consensus, referring back to the original trial, and in consultation with a third reviewer (HR). The study level risk of bias assessment was done using the Cochrane bias risk assessment tool[10] (Table 2 in Supplementary Material online). GRADE (Grading of Recommendation Assessment, Development and Evaluation) criteria[11] were used to assess the quality of evidence of estimates derived from NMA (Supplementary Table 3).

Data synthesis and analysis

The primary focus was on MACEs (a composite of myocardial infarction (MI), stroke and all-cause mortality). The secondary endpoints were MI, stroke, all-cause mortality, cardiovascular mortality, serious adverse events, musculoskeletal (MSK) adverse events, elevation of serum transaminases and serum creatine kinase levels. The definitions of the outcomes were taken as reported in the individual studies.

The Bayesian NMA was conducted using NetMetaXL 1.6.1 (Canadian Agency for Drugs and Technologies in Health; Ottawa, Canada) and winBUGS 1.4.3 (MRC Biostatistics Unit; Cambridge, United Kingdom). Outcomes were combined using the random effects

model (informative priors).[12] For all estimates, convergence was achieved at 40,000 iterations and autocorrelation was checked and confirmed. The inconsistency of the model was calculated as suggested by Lu and Ades.[13] We obtained a median estimate of odds ratio (OR) from the posterior distribution and reported it with 2.5th to the 97.5th centiles of the distribution (95% credible interval (CrI)). The assessment of between-study heterogeneity variances was interpreted as low ($\tau^2 = 0.04$), moderate ($\tau^2 = 0.14$) and high ($\tau^2 = 0.40$).[14] Markov chain Monte Carlo (MCMC) modeling was used to estimate the relative ranking probability of each treatment group.[15] "Rankograms" with surface under the cumulative ranking curve (SUCRA) were reported to provide a comparative hierarchy of efficacy and safety of the treatment groups.[16] A SUCRA is a numerical representation of the probability of effectiveness or safety, that is, a SUCRA of 90% means the treatment of interest has achieved 90% of effectiveness or the safety of that treatment relative to other groups. To assess the robustness of primary outcome findings, we conducted sensitivity analyses in secondary prevention trials and by excluding studies with unique populations (i.e. diabetes mellitus (DM), systolic heart failure, chronic kidney disease or renal transplant patients). Publication bias was assessed using Egger's regression test.

Results

This initial electronic search yielded a total of 6826 records and 16 studies were obtained from references of the relevant articles, out of which 3844 citations were duplicates, and 1736 studies were excluded at title and abstract level screening. In full text screening, 1223 records were removed based on study design (non-randomized studies or systematic review/meta-analyses), undesired outcomes and short follow-up duration (<6 months). Ultimately 39 studies[3,6,17–51] were included in this meta-analysis (Figure 1). A total of 189,116 patients (PCSK9 inhibitor (21,191 patients), ezetimibe (417 patients), ezetimibe plus statin (15,091 patients), statin (86,238 patients) and placebo (66,179 patients)) participated in this meta-analysis. The clinical characteristics of the participants are summarized in Supplementary Table 1. Briefly, mean age of the population was 61.2 ± 7.3 years and 64% were men. Baseline LDL-C was 132 ± 35 (mg/dL), 49% had coronary artery disease, 51% had hypertension and 24% had DM. The mean (SD) follow-up duration was 34.7 (23.5) months.

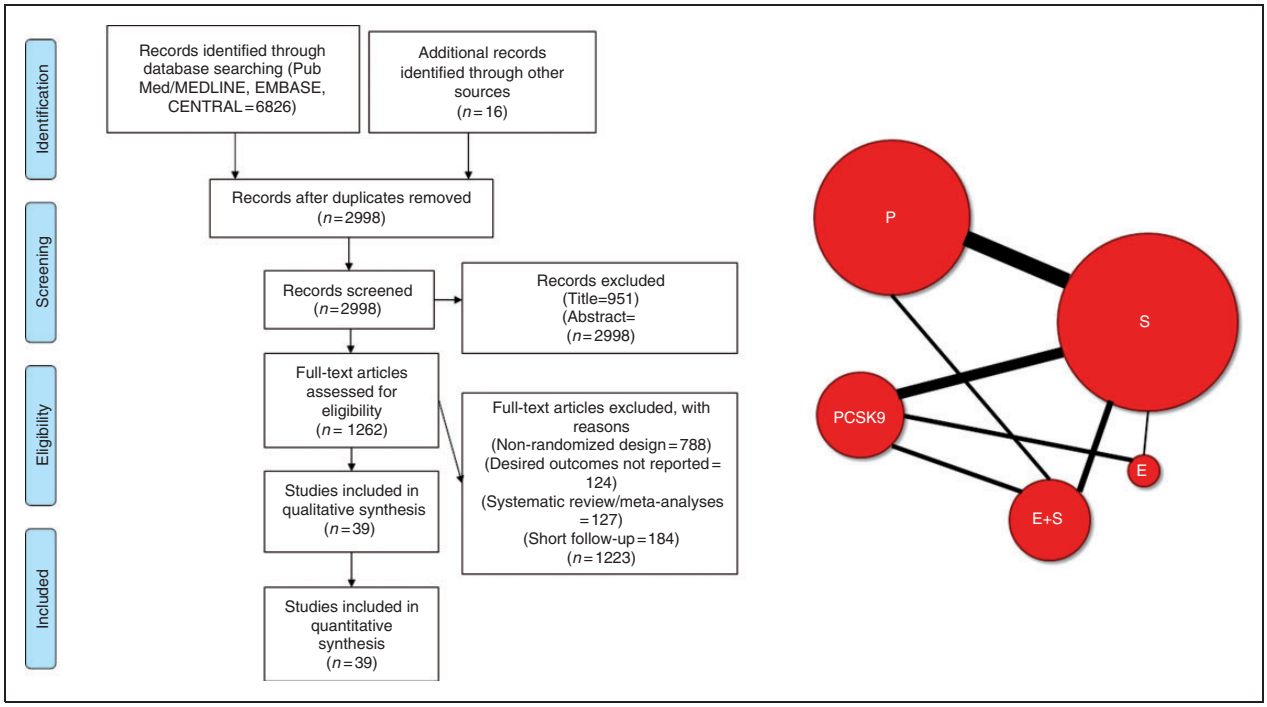

Figure 1. Search strategy using PRISMA statement and network diagram.
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension
Circle size represents sample size of the group.
E: ezetimibe; P: placebo; S: statins; PCSK9: PCSK9 inhibitors

MACE

Bayesian NMA suggested that PCSK9 inhibitors had the highest probability of having the lowest risk of MACE (SUCRA, 85%), followed by statins (SUCRA, 75%) and ezetimibe + statins (SUCRA, 51%). PCSK9 inhibitors were associated with significant 28% relative risk reduction compared with ezetimibe + statin (OR: 0.72; 95% CrI: 0.55–0.95; GRADE: moderate), 22% risk reduction compared with statin (OR: 0.78; 95% CrI: 0.62–0.97; GRADE: moderate) and 37% risk reduction compared with placebo (OR: 0.63; 95% CrI: 0.49–0.79; GRADE: high). Statins were associated with significant 19% risk reduction compared with placebo (OR: 0.81; 95% CrI: 0.75–0.87; GRADE: high). Statistical heterogeneity was low ($\tau^2 = 0.13$) (Figures 2 and 3). Sensitivity analyses of secondary prevention trials showed consistent superiority of PCSK9 inhibitors (SUCRA, 95%), followed by

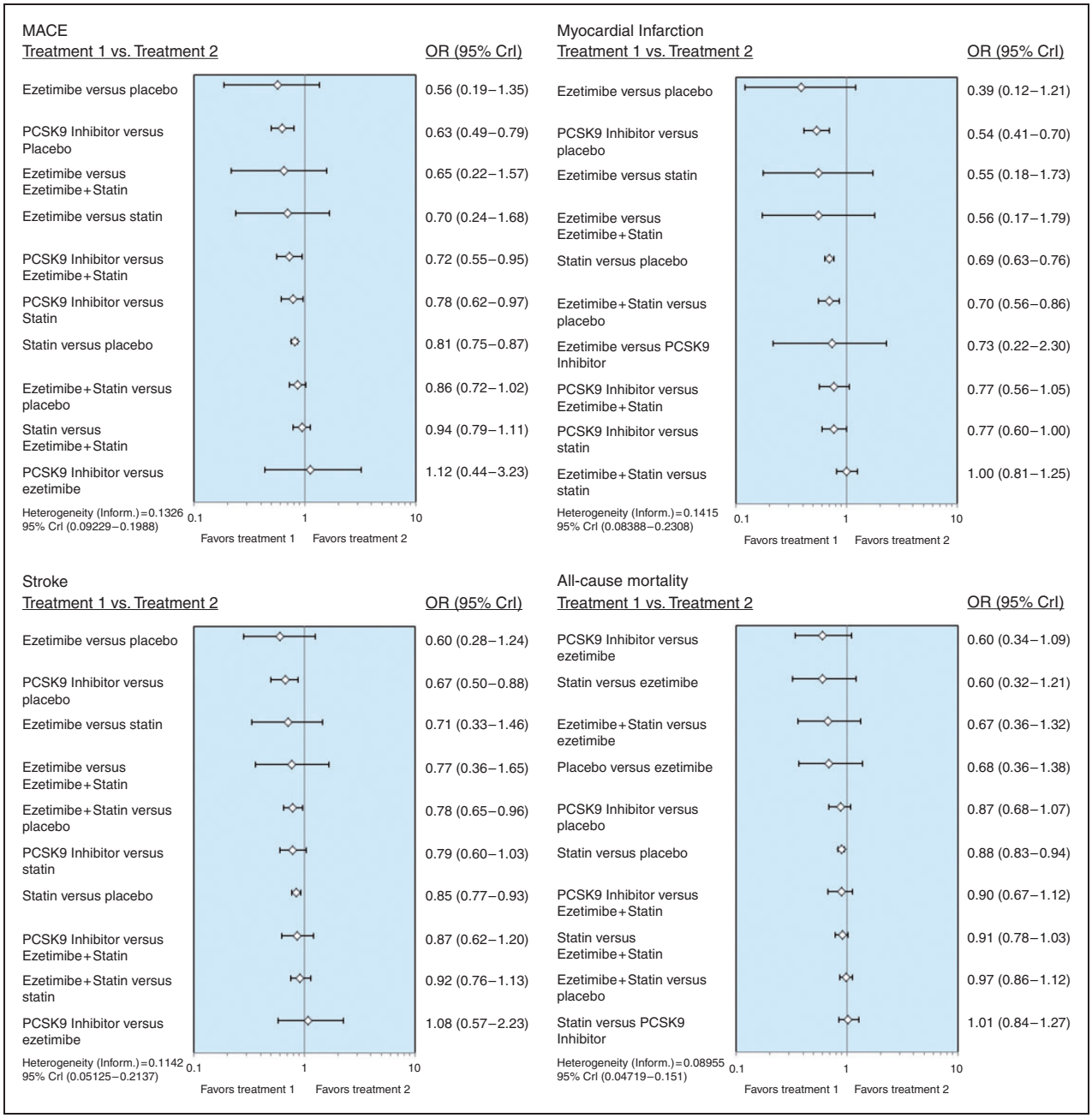

Figure 2. Forest plots showing comparison among treatment groups for MACE, myocardial infarction, stroke and all-cause mortality. MACE: major adverse cardiovascular event; OR: odds ratio; CrI: credible interval; PCSK9: PCSK9 inhibitors

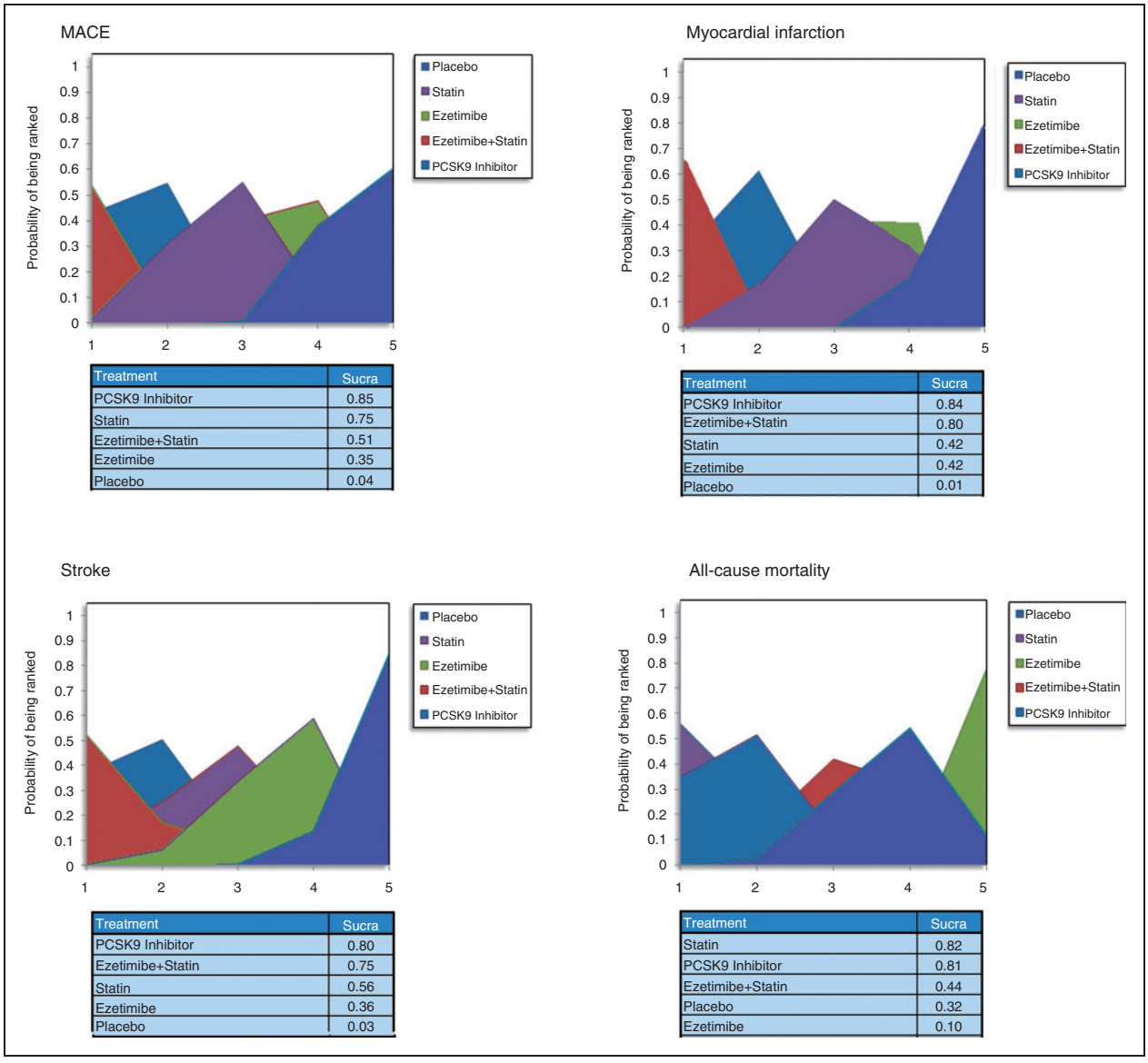

Figure 3. Rankograms showing probability analysis among treatment groups for MACE, myocardial infarction, stroke and all-cause mortality.
MACE: major adverse cardiovascular event

ezetimibe + statins (SUCRA, 59%) and statins (SUCRA, 45%) (Supplementary Figure 2). PCSK9 inhibitors remained the superior therapy after excluding patients with DM, systolic heart failure, chronic kidney disease or renal transplant patients (Supplementary Figure 3).

Secondary endpoints

Myocardial infarction. Bayesian NMA suggested that PCSK9 inhibitors had the highest probability of having the lowest rate of MI (SUCRA, 84%) followed by ezetimibe + statin (SUCRA, 80%) and statins (SUCRA, 42%). Compared with placebo, PCKS 9 inhibitors caused significant 46% relative risk reduction (OR: 0.54; 95% CrI: 0.41–0.70; GRADE: moderate), ezetimibe + statin caused 30% risk reduction (OR: 0.70; 95% CrI: 0.56–0.86; GRADE: moderate) and statins caused 31% risk reduction (OR: 0.69; 95% CrI: 0.63–0.76; GRADE: moderate) in MI. Statistical heterogeneity was moderate ($\tau^2 = 0.14$) (Figures 2 and 3).

Stroke. Bayesian NMA suggested that PCSK9 inhibitors had the highest probability of having the lowest rate of stroke (SUCRA, 80%), followed by ezetimibe + statin (SUCRA, 75%) and statins (SUCRA, 56%). Compared

with placebo, PCSK9 inhibitors reduced the relative risk of stroke by 33% (OR: 0.67; 95% CrI: 0.50–0.88; GRADE: high), ezetimibe + statins by 22% (OR: 0.78; 95% CrI: 0.65–0.96; GRADE: high) and statins by 15% (OR: 0.85; 95% CrI: 0.77–0.93; GRADE: high). Statistical heterogeneity was low ($\tau^2 = 0.11$) (Figures 2 and 3).

Mortality. Bayesian NMA demonstrated that statins had the highest probability of having the lowest rates of all-cause mortality (SUCRA, 82%), followed by PCSK9 inhibitors (SUCRA, 81%) and ezetimibe + statins (SUCRA, 44%). Compared with placebo, statins were associated with significant 12% relative risk reduction in all-cause mortality (OR: 0.88; 95% CrI: 0.83–0.94; GRADE: moderate). PCSK9 inhibitors had non-significant effect on all-cause mortality compared with placebo (OR: 0.87; 95% CrI: 0.68–1.07; GRADE: high). Statistical heterogeneity was low ($\tau^2 = 0.08$) (Figures 2 and 3). For cardiovascular mortality, statins were ranked as the best treatment for having the highest probability of reducing the cardiovascular mortality risk (SUCRA, 84%) followed by PSCK9 inhibitors (SUCRA, 78%) and ezetimibe + statins (SUCRA, 50%). Statins were associated with 16% relative risk reduction compared with placebo (OR: 0.84; 95% CrI: 0.77–0.90; GRADE: high) (Supplementary Figure 1). Statistical heterogeneity was low ($\tau^2 = 0.09$).

Safety endpoints. There were no significant differences among the treatment groups with regard to serious adverse events and MSK adverse events. Bayesian NMA ranked statins as the least safe treatment with regards to serum transaminase elevation (SUCRA, 2%) (Supplementary Figure 3). Compared with statins, ezetimibe (OR: 0.32; 95% CrI: 0.09–0.95; GRADE: moderate), placebo (OR: 0.56; 95% CrI: 0.29–0.91; GRADE: moderate) or PCSK9 inhibitor (OR: 0.59; 95% CrI: 0.32–0.97; GRADE: moderate) were associated with reduced risk of serum transaminases elevation. Statins were also ranked the least safe treatment in terms of serum creatine kinase elevation (SUCRA, 0) (Supplementary Figure 4). Compared with statins, PCSK9 inhibitors (OR: 0.45; 95% CrI: 0.28–0.70; GRADE: high), ezetimibe (OR: 0.46; 95% CrI: 0.22–0.82; GRADE: high) and placebo (OR: 0.49; 95% CrI: 0.30–0.79; GRADE: high) significantly reduced the risk of serum creatine kinase elevation. Heterogeneity was low to moderate for all of these estimates ($\tau^2 \leq 0.14$) (Figure 4).

Egger's regression test could not detect publication bias among different treatments (p-value (two tailed) $> .05$).

Discussion

In this Bayesian NMA of 39 RCTs with 189,116 patients, we report that PCSK9 inhibitors were ranked as the most effective treatment for reducing MACE, MI and stroke. PCSK9 inhibitors significantly reduced the risk of MACE compared with ezetimibe + statin and statins alone. PCSK9 inhibitors were consistently superior in sensitivity analyses for secondary prevention trials and after excluding diabetics, patients with heart failure, or renal disease. All the lipid lowering drugs significantly reduced the risk of MI and stroke compared with placebo. MCMC modeling demonstrated that statins had higher probability for reducing the risk of all-cause mortality and cardiovascular mortality. The treatment groups had no significant differences with regard to serious adverse events and MSK adverse events. Statins were ranked as the least safe treatment in terms of worsening liver function tests and elevation of serum creatine kinase levels.

Statins are known to provide up to 25% relative risk reduction in MACEs per unit decrease in LDL-C.[2,52] The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial showed that the incremental 20–25% reduction in LDL-C achieved by adding ezetimibe to statins yielded the expected cardiovascular benefits.[3] On the other hand, various pooled analyses had shown that PCSK9 inhibitors provided more robust reduction in LDL-C compared with ezetimibe or placebo.[4,5] Lepinski et al. reported a significant 57% mean reduction in LDL-C by PCSK9 inhibitors compared with placebo and 36.1% reduction compared with ezetimibe.[4] Similarly, Toth and colleagues showed 54% to 74% mean reduction by PCSK9 inhibitors versus placebo and 26% to 46% reduction versus ezetimibe.[5] However, despite this significant lowering of LDL-C, a relatively diminished clinical efficacy of PCSK9 therapy was observed in former reports.[4,5] As cardiovascular events are rare events, which usually require prolonged drug exposure for significant differences to emerge, studies with limited follow-up duration are likely to underestimate treatment effects. Therefore, to demonstrate this effect, we restricted our inclusion criteria to studies of at least six months' follow-up duration.

While our probability analysis ranking PCSK9 inhibitors as the best treatment for reducing MACEs validate "lower is the better" notion, the superiority of statins over ezetimibe + statin appeared counter intuitive to our hypothesis. This discrepancy can be explained by the fact that in overall analysis, statin data was more extensive compared with other treatments, whereas ezetimibe was the smallest group and thus had relatively less power to detect the outcome differences. However, more focused sensitivity analysis of secondary prevention trials reassured our hypothesis by ranking PCSK9 inhibitors as the most effective therapy, followed by ezetimibe + statins and then statins as third ranked treatment in prevention of MACE. On the

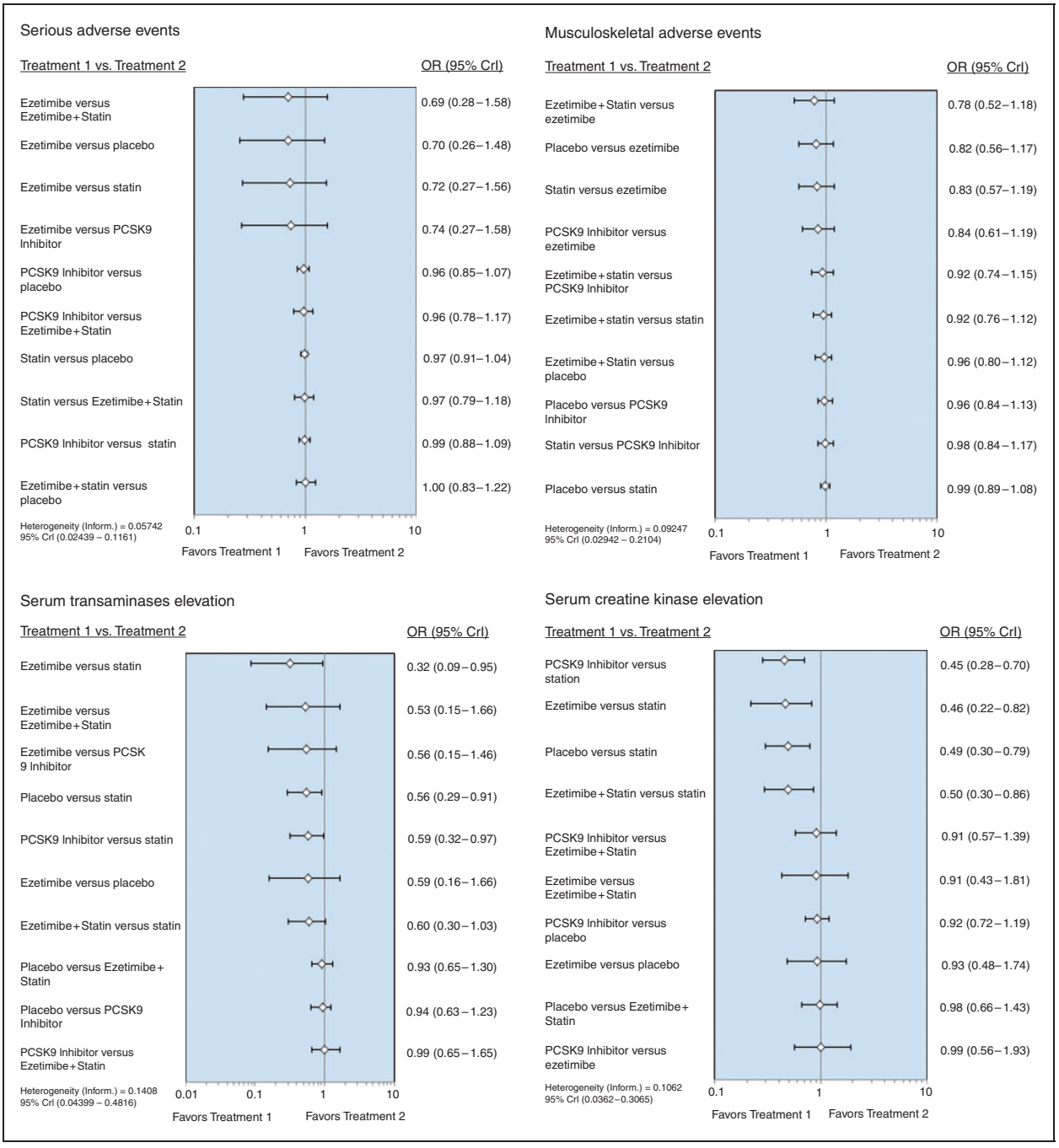

Figure 4. Forest plots showing comparison among treatment groups for serious adverse events, musculoskeletal adverse events, elevation in serum transaminases and creatine kinase levels.
MACE: major adverse cardiovascular event; OR: odds ratio; CrI: credible interval; PCSK9: PCSK9 inhibitors

same note, statins have invariably shown to improve survival in both primary and secondary prevention trials, whereas, the majority of PCSK9 trials, including the well powered FOURIER trial, failed to demonstrate mortality benefit by evolocumab,[6] our report is in line with the published data stating that statins were superior to other treatments for better mortality outcomes.

The European Society of Cardiology guidelines suggest that PCSK9 inhibitors should be considered in high risk patients with high LDL-C who are either refractory to maximal tolerated statins and in combination with ezetimibe or statin intolerant patients.[53] The American College of Cardiology guidelines recommend PCSK9 inhibitors only for patients with clinical CVD failing to achieve therapeutic targets while already

taking maximal tolerated doses of statin therapy and for subjects with baseline LDL-C levels ≥ 190 mg/dL even in the absence of clinical CVD.[54] However, our report generates the possibility that PCSK9 inhibitors might serve as a more effective and safer option compared with a conventional statin or ezetimibe + statin based approach for MACE advantage. One safety concern regarding PCSK9 inhibitor therapy is that extreme LDL-C reduction may generate neurocognitive adverse events. A recent meta-analysis by Khan and colleagues[55] showed the enhanced risk of neurocognitive adverse events (OR, 2.85; 95% CI: 1.34-6.06) in subgroup analysis of two trials. In our NMA, we could not assess this outcome due to exceedingly low events reported in long-term follow-up studies. However, the EBBINGHAUS study[56] and a more recent meta-analysis by Schmidt et al.[57] have not demonstrated PCSK9 inhibitor-related neurocognitive concerns at extended follow-up duration, which advocates the long-term safety of these agents.

The strength of this study lies in the use of a sophisticated statistical approach to assess clinical differences in the entire group of relevant lipid lowering strategies. The results are robust, as overall there is low to moderate statistical heterogeneity and consistency of the outcomes is preserved in sensitivity analyses. The GRADE approach demonstrated moderate to high quality of evidence for most of the estimates. However, there are certain limitations. First, the NMA was generated on study-level information and was not adjusted for patient-level data; therefore, subgroup analyses could not be performed. Second, as appreciated earlier, the statin data was more extensive compared with other treatments, whereas ezetimibe was the smallest group. Third, another source of heterogeneity is the lipid lowering indication for the trials (i.e. for primary or secondary prevention). Although we performed a separate analysis on secondary prevention trials for MACE endpoint, the secondary endpoints were not analyzed separately, which can affect the results in this meta-analysis. Fourth, while the statins trials were well powered studies, the majority of primary prevention trials of PCSK9 inhibitors or ezetimibe were not adequately powered to assess cardiovascular outcomes. Fifth, there was a wide variation in drugs and doses across the treatments, specifically in the statin trials. Thus, a comparison of PCSK9 inhibitors with lower potency statins could be predicted to show more favorable results than if PCSK9 inhibitors were compared with more high potency statin trials. Sixth, due to sparseness of data, we could not analyze some important end points such as neurocognitive adverse events or immunological or allergic reactions. Seventh, we did not assess the LDL-C lowering potential of the treatment groups as this aspect has been extensively studied in prior meta-analyses.[4,5,52,57] Eight, we did not perform cost effective analysis of these agents and since cost effectiveness of PCSK9 inhibitors based on their LDL-C lowering potential is an issue,[58] this is a potential limitation. Finally, NMA is theoretically limited due to direct and indirect comparisons of the interventions. Therefore, our report should be viewed primarily as hypothesis generating.

In summary, we conclude that in view of substantial reduction in LDL-C compared with other lipid lowering drugs, PCSK9 inhibitors significantly provided MACE benefits without causing serious safety concerns. Statins are superior to other lipid lowering medications for improving total or cardiovascular survival. Our review enables clinicians to determine the degree of additional cardiovascular protection provided by PCSK inhibitors beyond that provided by ezetimibe, statins or combination of ezetimibe and statins. This report also highlights the necessity of long-term follow-up trials to assess the protective effects of PCSK9 inhibitors on hard estimates in comparison with other lipid lowering therapies.

Author contribution

SUK contributed to the conception and design of the work. ST, HR, FN and IRB contributed to the data acquisition, analysis and interpretation of data for the work. SUK and HR drafted the manuscript. SS, EK, HA and RK critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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