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Complete List of Authors:	Deng, changjiang; Xinjiang Medical University Affiliated First Hospital, Department of Cardiology Yan, Ju; Xinjiang Medical University Affiliated First Hospital, The First Department of Coronary Artery Disease Zheng, Ying-Ying; Xinjiang Medical University Affiliated First Hospital Wu, Ting-Ting; Xinjiang Medical University Affiliated First Hospital Pan, Ying; Xinjiang Medical University Affiliated First Hospital, Department of Cardiology Hou, Xian-Geng; Xinjiang Medical University Affiliated First Hospital Wang, Si-Fan; Xinjiang Medical University Affiliated First Hospital, Department of Cardiology Sirajidin, Subinur; Xinjiang Medical University Affiliated First Hospital Aimaitijiang, Mikereyi; Xinjiang Medical University Affiliated First Hospital Xie, Xiang; Xinjiang Medical University Affiliated First Hospital, Department of Cardiology
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Effectiveness of lipid-lowering therapy on mortality and major adverse cardiovascular event outcomes in patients undergoing percutaneous coronary intervention: a network meta-analysis of randomized controlled trials

Chang-Jiang Deng, Ju Yan, Ying-Ying Zheng,Ting-Ting Wu, Ying Pan, Xian-Geng Hou,Si-Fan Wang, Subinur·Sirajidin, Mikereyi.Aimaitijiang,Xiang Xie

Department of Cardiology, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, 830011, P.R. China.

Correspondence authors:

Xiang Xie, No. 137, Liyushan Road, Department of Cardiology, First Affiliated Hospital of Xinjiang Medical University, Urumqi, 830011 P.R., China. Tel: +8609914366168; Email: xiangxie999@sina.com

Abstract

Objective

This study will assess the benefits of different lipid-lowering regimens on the risk of MACEs and mortality in the post-PCI population by network meta-analysis.

Methods

Public literature databases, including PubMed, Embase, and the Cochrane Library, were searched from inception to August 2022. Randomized controlled trials (RCTs) on lipid-lowering regimens in post-PCI populations were included and analyzed. The outcomes were the incidence of all-cause mortality and MACE, whether reported as

dichotomous or hazard ratio (HR) statistics.

Results

Thirty-nine RCTs were included. For MACEs, alirocumab plus rosuvastatin (OR: 0.18; 95% CI: 0.07-0.44;), evolocumab plus ezetimibe and statins (OR: 0.19; 95% CI:0.06-0.59), eicosapentaenoic acid (EPA) plus pitavastatin (HR: 0.67; 95% CI: 0.49-0.96), and icosapent ethyl plus statins (HR: 0.73; 95% CI: 0.62-0.86) had significant advantages and relatively high rankings. For mortality, rosuvastatin (OR: 0.30; 95% CI: 0.11-0.84), ezetimibe plus statins (OR: 0.55; 95% CI: 0.43-0.89) and icosapent ethyl plus statins (OR: 0.66; 95% CI: 0.45-0.96) had significant advantages compared to the control.

Conclusion

EPA, especially icosapent ethyl, plus statins had a beneficial effect on reducing the risk of MACEs and mortality in post-PCI patients. PCSK9i plus statins was able to reduce the risk of MACEs, but the risk of mortality remained unclear.

Key words:lipid-lowering therapy, major adverse cardiovascular events, mortality, network meta-analysis

Introduction

Acute coronary syndrome (ACS) is a term used to refer to a range of conditions associated with acute myocardial ischemia and/or infarction, which are usually due to coronary artery occlusion and acute ischemic necrosis of the myocardium due to progression of coronary atherosclerotic lesions[1, 2]. Emergency percutaneous coronary

intervention (PCI) can quickly restore myocardial perfusion[3]. Although the development of technological and procedural PCI have resulted in substantial improvements in clinical outcomes, recurrent coronary events may still occur after PCI[4].

The view of "residual cardiovascular risk" was introduced because MACE still occurs in some patients who received PCI during follow-up. PCI can treat focal manifestations of systemic progressive disease, but the residual risk of acute coronary syndrome is largely related to the systemic proatherosclerotic effect of poorly controlled cardiovascular risk factors[5]. Lowering lipid levels, especially LDL-C, can halt the progression of coronary atherosclerosis and improve cardiovascular outcomes. Based on this view, it is believed that long-term optimal lipid-lowering therapy is effective in reducing long-term cardiovascular events after PCI. However, the view was still subject to challenges.

Based on data from the “Korea Acute Myocardial Infarction Registry”, the proponents concluded that patients treated with statins had significantly lower rates of MACE, all-cause death, and cardiac death during the 2-year follow-up period after PCI application[6]. However, a study of postoperative follow-up of PCI patients enrolled in the Melbourne Interventional Group registry concluded that statins have no significant benefit to MACEs after PCI [6]. The controversy may be based on two reasons: on the one hand, is that the optimal lipid reduction target may not be achieved by using single statins [7, 8]. On the other hand, long-term high-dose application of statins

increases the risk of intracerebral hemorrhage and other side effects [9, 10].

There is a consensus on preloading high-dose statins to reduce MACEs in the perioperative period with PCI [11, 12]. However, there is still insufficient evidence for the continued application of lipid-lowering drugs to reduce the risk of long-term MACE and mortality. This study will assess the benefits of different lipid-lowering regimens on the risk of MACEs and mortality in the post-PCI population by network meta-analysis.

Methods

This study was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Patient and Public Involvement

None

Search strategy

Public literature databases, including PubMed, Embase, and the Cochrane Library, were searched from inception to August 2022 without language restrictions using the following search terms: (lipid-lowering or statin or simvastatin or rosuvastatin or atorvastatin or fluvastatin or lovastatin or pravastatin or pitavastatin or mevastatin or ezetimibe or “eicosapentaenoic acid” or “icosapent ethyl” or “bempedoic acid” or fibrate or bezafibrate or gemfibrozil or fenofibrate or ciprofibrate or evolocumab or

alirocumab or evinocumab or volanesorsen or vupanorsen or pelacarsen or olezarsen or inclisiran or olpasiran) and ("percutaneous coronary intervention" or "coronary angioplasty") and (random* or randomized or randomized). The references of relevant systematic reviews and meta-analyses were also searched to avoid omissions. The two authors conducted literature retrieval independently, and any conflicts were resolved through discussion with the third author.

Inclusion and exclusion criteria

The literature was included if it met the following criteria: 1, the study adopted a randomized controlled study design; 2, the study included patients who received PCI surgery or reported the subgroup of the population that received PCI; 3, the lipid-lowering regimen was applied to the population of the intervention group; 4, the control group used a different lipid-lowering agent or regimen; and 5, the study reported the outcome of mortality and/or MACE. Exclusion criteria: 1, as preloading of statins before PCI had clear benefits, to determine whether application of lipid-lowering drugs after PCI also had beneficial effects. This work excluded the study on the preloading application of lipid-lowering drugs before PCI; 2, although high-dose lipid-lowering agents, such as statins, have a better lipid-lowering effect, long-term application may bring potential side effects [9, 13]. In this study, all agents were considered to be applied with reasonable doses, and dose–response studies were excluded. In addition, repeatedly published studies, protocols, conference abstracts, reviews, comments and editorials were also excluded.

Data extraction and quality assessment

Two authors independently extracted the information from the included studies. The contents include the name of the first author, publication year, study location, sample size (population received PCI), study abbreviation and registration number, lipid-lowering intervention and control, and follow-up time.

The outcomes analyzed were the incidence of all-cause mortality and MACE, whether reported as dichotomous or hazard ratio (HR) statistics based on Cox regression. The MACE outcome was selected to most closely approximate the composite endpoint, including mortality, MI, stroke, coronary revascularization, and restenosis. Study quality was assessed by two investigators using the Cochrane risk of bias assessment tool, which included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential biases.

Statistical analysis

For each direct paired comparison, we used the odds ratios and their 95% confidence intervals (CIs) for dichotomous outcomes. The hazard ratios and their 95% CIs based on Cox regression results were also pooled for reporting. We conducted frequentist network meta-analysis (NMA) using random effect models with restricted maximum likelihood estimation to quantify network heterogeneity. The Q statistic was used to

assess the sum of statistics for heterogeneity (within designs) and for overall inconsistency (between designs)[14]. The ranking probabilities of each regimen were estimated using the surface under the cumulative ranking curve (SUCRA), and a comparison-adjusted funnel plot was used to examine potential publication biases in NMA. P values of less than 0.05 were considered to be statistically significant. The NMA was performed using R language with the "netmeta" package.

Results

After removing duplications, we obtained 1588 literature items. After a screen of the titles and abstracts, 1515 irrelevant studies were excluded. Seventy-three articles were screened for full text. The following articles were excluded: dose–response studies (8), no PCI population or subgroup was reported (6); no mortality or MACE-related outcomes were reported (6); repeated publication (5); study related to preloading of lipid-lowering agents (4); study not related to lipid-lowering agents (3); protocol (1); non-RCT design (1). Finally, 39 articles were included containing 54478 patients after PCI [15-53] (Figure 1).

Among the included studies, the publication period ranged from 1991 to 2022. The research locations were mainly in Asia (China, Japan and South Korea), Europe (Netherlands, France, and Italy), America, and multiple centers. There were 10 studies with sample sizes greater than 1000 patients. There were also 22 studies with publicly available clinical study registration numbers (Table 1). In terms of design quality, all

included studies were RCTs. Therefore, the design quality is generally high. The main factors potentially affecting design quality were the blinding of participants and personnel and blinding of outcome assessment (Figure 2). However, as the desired outcomes were mortality and MACE, the subjective factors of the investigator had little influence on the outcomes.

Table 1. The characteristics of included studies

Study	Location	Sample size	Abbreviation	Register ID	Intervention	Control	Follow-up#
Lorenz Räber 2022 [15]	European	300	PACMAN-AMI	NCT03067844	Alirocumab;rosuvastatin	Placebo;rosuvastatin	52W
Peterson, B. E. 2022 [16]	Multicenter	3408	REDUCE-IT PCI	NCT01492361	Icosapent ethyl;statins	Placebo;statins	4.8Y
Remo H.M. Furtado 2022 [17]	Multicenter	17073	FOURIER	NCT01764633	Evolocumab;statins	Placebo;statins	2.2Y
Tomoaki Okada 2022 [18]	Japan	102	-	UMIN000028729	Evolocumab;pitavastatin	Pitavastatin	4W
Yan Hao 2022 [19]	China	136	-	-	Evolocumab;atorvastatin;ezetimibe	Ezetimibe;atorvastatin	3M
Deng YF 2021 [20]	China	90	-	-	Ezetimibe;atorvastatin	Atorvastatin	1Y
Sun C 2021 [21]	China	171	-	ChiCTR-IPR-17012219	Ezetimibe;rosuvastatin	Rosuvastatin	3M
Weifeng He 2020 [22]	China	192	-	-	Atorvastatin vs. Rosuvastatin vs. Simvastatin	-	6M
Kiyoshi Hibi 2018 [23]	Japan	128	Ezetimibe-ACS	NCT00549926	Ezetimibe;pitavastatin	Pitavastatin	1Y
Eui Im 2017 [24]	Korea	2000		NCT01557075	Atorvastatin	Pravastatin	1Y
Hagiwara N 2017 [25]	Japan	1734	HIJ-PROPER	UMIN000002742	Ezetimibe;pitavastatin	Pitavastatin	36M
J Guo 2017 [26]	China	137	-	-	Rosuvastatin	Control	1Y
Wang YB 2017 [27]	China	132	-	ChiCTR-IPR-15007035	Pitavastatin	Atorvastatin	6M
Watanabe T 2017 [28]	Japan	193	CHERRY	UMIN000002815	EPA;pitavastatin	Pitavastatin	6-8M
Zhi Liu 2017 [29]	China	102	-	-	Ezetimibe;atorvastatin	atorvastatin 20mg/d	1Y
Kazumasa Nosaka 2016 [30]	Japan	241	-	UMIN000016723	EPA;pitavastatin	Pitavastatin	1Y
Kensuke Matsushita 2016 [31]	Japan	118	Yokohama-ACS	NCT00549926	Atorvastatin vs. Pitavastatin vs. Pravastatin vs. Fluvastatin	-	10.3M
Christopher P Cannon 2015 [32]	Multicenter	12941	IMPROVE-IT	NCT00202878	Ezetimibe;simvastatin	Simvastatin	6M
Kenichi Tsujita 2015 [33]	Multicenter	246	PRECISE-IVUS	NCT01043380	Ezetimibe;atorvastatin	Atorvastatin	1Y
Stephen J. Nicholls 2015 [34]	Multicenter	3295	VISTA-16	NCT01130246	Varespladib;atorvastatin	Placebo;atorvastatin	6M

Zhang JR 2015 [35]	China	104	-	-	Atorvastatin	Rosuvastatin	6M
Mario Leoncin 2014 [36]	Italy	333	PRATO-ACS	NCT01185938	Rosuvastatin	Control	6M
Hiroyuki Takano 2013 [37]	Japan	458	PEARL	UMINC000000428	Pitavastatin	Control	35.5M
Tsuyoshi Nozue 2013 [38]	Japan	164	TRUTH	UMIN000004627	Pitavastatin	Pravastatin	2Y
Jean-Marc Lablanche 2010 [39]	Multicenter	887	CENTAURUS	NCT00296387	Rosuvastatin	Atorvastatin	3M
C. Michael Gibson 2009 [40]	US	2868	PROVE IT-TIMI 22	NCT00382460	Atorvastatin	Provastatin	2Y
Han Yaling 2009 [41]	China	1275	-	NCT00405717	Atorvastatin	Provastatin	1Y
Takafumi Hiro 2009 [42]	Japan	307	JAPAN-ACS	NCT00242944	Pitavastatin	Atorvastatin	1Y
Tomotaka Dohi 2009 [43]	Japan	180	Extended-ESTABLISH trial	-	Atorvastatin	Control	4Y
Toru Toi 2009 [44]	Japan	160	-	-	Pitavastatin	Atorvastatin	17D
Xu Kai 2007 [45]	China	648	-	-	Atorvastatin	Control	2Y
Bae JH 2004 [46]	Korea	205	-	-	Atorvastatin	Control	6M
Patrick W J C Serruys 2002 [47]	Multicenter	1677	LIPS	-	Fluvastatin	Placebo	3.9Y
Han J.G.H. Mulder 2000 [48]	Netherland	201	REGRESS	-	Pravastatin	Placebo	2Y
Greg C. Flaker 1999 [49]	Multicenter	1154	CARE trial	-	Pravastatin	Placebo	6Y
MICHEL E. BERTRAND 1997 [50]	France	695	PREDICT	-	Pravastatin	Placebo	6M
J H O'Keefe Jr 1996 [51]	US	200	APPLE	-	Probucol;lovastatin	Placebo	6M
Haruhiko Onaka 1994 [52]	Japan	66	-	-	Pravastatin	Control	5M
Rakesh Sahni 1991 [53]	US	157	-	-	Lovastatin	Control	6M

Abbreviations: EPA: eicosapentaenoic acid.

#: Follow-up period: Y: years; M: months; W: weeks; D: days

As two studies did not specify the types of statins, the network meta-analysis will be divided into two parts. One part was analyzed based on specific types of statins, and the other was based on taking statins as a whole. For the dichotomous results of MACE, the NMA based on specific types of statins included 18 lipid-lowering regimens. The Q test for heterogeneity was $p = 0.07$, and for inconsistency, it was $p =$

0.16, indicating no evidence for heterogeneity and inconsistency in the NMA.

In pairwise comparisons with the control, alirocumab plus rosuvastatin (OR: 0.18; 95% CI: 0.07-0.44; SUCRA: 0.94), evolutionab plus atorvastatin and ezetimibe (OR: 0.18; 95% CI: 0.05-0.63; SUCRA: 0.90), ezetimibe plus rosuvastatin (OR: 0.29; 95% CI: 0.11-0.76; SUCRA: 0.80) have significant advantages and relatively high SUCRA rankings. No potential publication bias was found according to the comparison-adjusted funnel plot (Figure 3).

In the NMA based on taking statins as a whole, ten regimens were analyzed. Evolocumab plus ezetimibe and statins (OR: 0.19; 95% CI: 0.06-0.59; SUCRA: 0.92), alirocumab plus statins (OR: 0.27; 95% CI: 0.13-0.59; SUCRA: 0.87), and coscapent ethyl plus statins (OR: 0.39; 95% CI: 0.25-0.62; SUCRA: 0.72) have significant advantages and relatively high SUCRA rankings. No potential publication bias was found.

For the HR results of MACEs, the NMA based on specific types of statins included nine regimens. The Q test for heterogeneity was $p = 0.964$ and because the network comparisons lack loops. Therefore, the results were considered consistent. Compared to the control, eicosapentaenoic acid (EPA) plus pitavastatin (HR: 0.67; 95% CI: 0.49-0.96; SUCRA: 0.91), atorvastatin (HR: 0.76; 95% CI: 0.63-0.90; SUCRA: 0.83), and varespladib plus atorvastatin (HR: 0.77; 95% CI: 0.61-0.97; SUCRA: 0.77) have significant advantages and relatively high SUCRA rankings. Potential publication bias

was not analyzed due to a smaller number of included studies.

In the NMA based on taking statins as a whole, seven regimens were analyzed. EPA plus statins (HR: 0.60; 95% CI: 0.42-0.85; SUCRA: 0.96) and icosapent ethyl plus statins (HR: 0.73; 95% CI: 0.62-0.86; SUCRA: 0.81) had significant advantages over the control.

For the dichotomous results of mortality, the NMA based on specific types of statins included 17 lipid-lowering regimens. The Q test for heterogeneity was p = 0.78, and for inconsistency, it was p = 0.99. Due to the rare occurrence of events, the results of the comparison were low precision with a large standard error. Compared to the control, only rosuvastatin (OR: 0.30; 95% CI: 0.11-0.84; SUCRA: 0.79) showed a significantly better effect. Ezetimibe plus rosuvastatin had a relatively high SUCRA ranking, but there was no significant difference compared to the control (OR: 0.14; 95% CI: 0.02-1.26; SUCRA: 0.86). No potential publication bias was found (Figure 4).

In the NMA based on taking statins as a whole, nine regimens were analyzed. Ezetimibe plus statins (OR: 0.55; 95% CI: 0.43-0.89; SUCRA: 0.75) and icosapent ethyl plus statins (OR: 0.66; 95% CI: 0.45-0.96; SUCRA: 0.63) had significant advantages compared with the blank control group. No potential publication bias existed. NMA analysis was not performed due to the small number of studies reporting HR for mortality (Figure 5).

Discussion

This study analyzed the benefits of lipid-lowering therapy on mortality and MACE outcomes in patients who received PCI by network meta-analysis. The results showed that several lipid-lowering regimens could reduce the risk of MACEs compared with the blank control. Icosapent ethyl plus statins had the benefit of reducing both the risk of MACEs and mortality. However, EPA plus statins had more advantages in reducing the risk of MACEs. Of note, based on the current evidence, alirocumab and evolocumab plus statins had obvious advantages in reducing the risk of MACEs but had no obvious benefit in reducing the risk of mortality.

EPA is a long-chain omega-3 polyunsaturated fatty acid. Long-term intake of EPA can reduce the residual cardiovascular risk to reduce the risk of MACEs[54]. In terms of pathological mechanisms, EPA combined with pitavastatin can reduce the lipid volume of coronary artery plaque and total atherosclerotic plaque volume in patients who receive PCI, which may be the reason for the reduced risk of MACEs [55].

Icosapent ethyl is a highly purified and stable eicosapentaenoic acid ethyl ester that has potential higher anti-inflammatory, antioxidant, plaque stability and cell membrane stability effects [56]. In the NMA results, icosapent ethyl plus statins had significant benefits for either mortality or MACEs in patients who received PCI, which was an ideal regimen for the population.

Ezetimibe inhibits the absorption of cholesterol and has a synergistic lipid-lowering pharmacological effect with statins to further reduce the risk of death and MACE. In particular, when combined with rosuvastatin, it has a stronger lipid-lowering effect with a high safety profile without the risk of drug interactions [57]. Our NMA results also showed that it can reduce the risk of MACE and mortality. According to the guidelines for the management of dyslipidemia from the European Society of Cardiology and the European Atherosclerosis Society, ezetimibe was recommended if the LDL-C level was not reached [58, 59]. The American College of Cardiology guidelines also recommend adding ezetimibe when using maximally tolerated statin therapy and if LDL-C levels remain ≥ 70 mg/dL [60]. These benefits have also been demonstrated in the secondary prevention of PCI.

Alirocumab and evolumab are both proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), which can increase the level of LDL receptor in the liver, thus improving the ability of the liver to bind LDL-C and reducing the level of peripheral LDL-C [61]. There was also a synergistic lipid-lowering pharmacological effect when PCSK9i was combined with statins that significantly reduced LDL-C and atherosclerosis event risk; however, there was still controversy regarding the mortality risk reduction [62]. It has been suggested that the powerful effect of PCSK9I on reducing LDL-C predisposes patients to hypocholesterolemia, which will increase the risk of cerebral hemorrhage [63, 64]. On the other hand, PCSK9i could not reduce serum

inflammatory factors, suggesting that it may not reduce the risk of residual inflammation in the post-PCI population [65].

In the results of this study, lipid-lowering therapy strategies had general advantages in reducing MACE risk. However, for all-cause mortality, the advantage of lipid-lowering therapy was not obvious. Based on dichotomous outcomes of mortality, some strategies may even have a tendency to increase the mortality risk. This challenges the opinion that lipid-lowering therapy is recommended after PCI [66]. A large sample size retrospective study suggests that statins can reduce the risk of all-cause death in patients with coronary artery disease undergoing PCI, regardless of personal cholesterol levels [67]. Alternatively, the "Lipid Paradox" view has been proposed and indicated that higher levels of LDL-C and triglycerides on admission are associated with better clinical outcomes. Especially in patients with ST-elevation myocardial infarction, lower LDL-C levels were associated with worse mortality outcomes [68]. However, this view is also controversial [69].

On the other hand, it is possible that the contribution of LDL-C reduction to the risk of mortality outcomes is obscured by the other confounding factors. For example, inflammatory status may also have an important impact on patient mortality risk. In a cohort of post-PCI patients with low LDL-C levels, residual inflammatory risk also had a significant effect on overall mortality [70]. C-reactive protein can also predict long-term mortality in post-PCI patients independent of LDL-C levels [71]. In addition,

cardiac remodeling also has an important impact on the survival outcome of people after PCI [72].

In conclusion, the results of this study suggest that EPA, especially icosapent ethyl, plus statins had a beneficial effect on reducing the risk of MACEs and mortality in post-PCI patients. PCSK9i plus statins was able to reduce the risk of MACEs, but the risk of mortality remained unclear.

There are still several limitations in this study. First, this study was based on the study level instead of the individual level, making it difficult to consider the individual confounding factors in the analysis. Second, two included studies did not specify the type of statins, so our study had to be analyzed separately according to whether all statins were considered as a whole. Third, the criteria for defining MACEs varied among studies that contributed to heterogeneity among the study results. Fourth, many included studies reported only dichotomous outcomes but did not report the HR results, resulting in the incompleteness of the relevant analysis results.

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Author contributions

Chang-Jiang Deng completed the manuscript, Ju Yan, Ting-Ting Wu and Ying Pan guided the data analysis and the production of the figures, All the authors read and approved the fnal manuscript.

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Availability of data and materials

the datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study does not involve human participants and ethical approval was not required.

Consent for publication

not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figure 1. Flowchart of the study selection process for eligible studies

Figure 2. Methodological quality assessment of included studies

Figure 3. Network plots of comparisons for major outcomes included in the analyses. A: dichotomous results of MACE based on specific types of statins; B: dichotomous results of MACE based on taking statins as a whole; C: hazard ratio results of MACE based on specific types of statins; D: hazard ratio results of MACE based on taking statins as a whole; E: dichotomous results of mortality based on specific types of statins; F: dichotomous results of mortality based on taking statins as a whole.

Figure 4. Forest plots of lipid-lowering therapy compare to control for outcomes in network meta-analysis with SUCRA ranking results. A: dichotomous results of MACE based on specific types of statins; B: dichotomous results of MACE based on taking statins as a whole; C: hazard ratio results of MACE based on specific types of statins; D: hazard ratio results of MACE based on taking statins as a whole; E: dichotomous results of mortality based on specific types of statins; F: dichotomous results of mortality based on taking statins as a whole.

Figure 5. The comparison-adjusted funnel plot for assessing all main outcomes. A: dichotomous results of MACE based on specific types of statins; B: dichotomous results of MACE based on taking statins as a whole; C: dichotomous results of mortality based on specific types of statins; D: dichotomous results of mortality based

on taking statins as a whole.

Authors and Afliations

Chang-Jiang Deng, Ju Yan, Ying-Ying Zheng,Ting-Ting Wu, Ying Pan, Xian-Geng Hou,Si-Fan Wang, Subinur·Sirajidin, Mikereyi·Sirajidin,Xiang Xie

Chang-Jiang Deng
1187229853@qq.com

Xian-Geng Hou
380138554@qq.com

Ju Yan
yyjj2017@163.com

Si-Fan Wang
562654119@qq.com

Ying-Ying Zheng
zhengying527@163.com

Subinur·Sirajidin
496568064@qq.com

Ting-TingWu

Mikereyi·Aimaitijiang
1255723526@qq.com

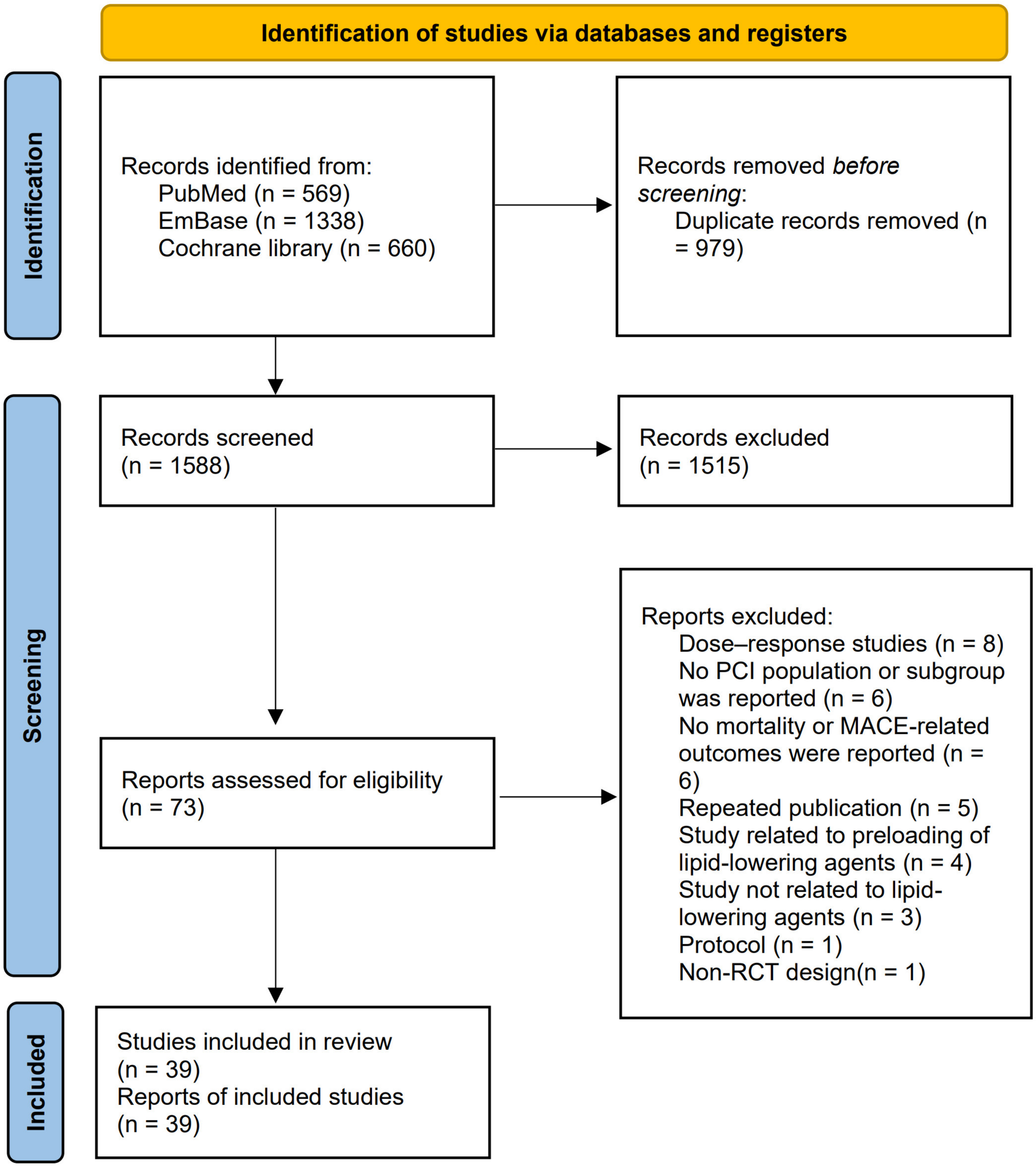
3195676352@qq.com

Ying Pan
2475854195@qq.com

Xiang Xie
xiangxie999@sina.com

Department of Cardiology, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, 830011, P.R. China.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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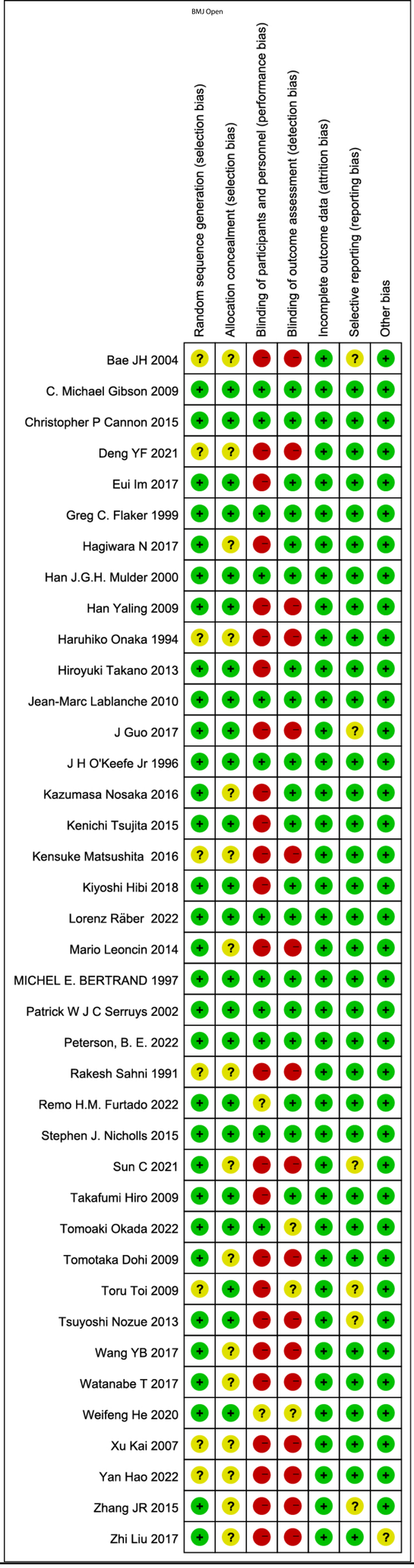

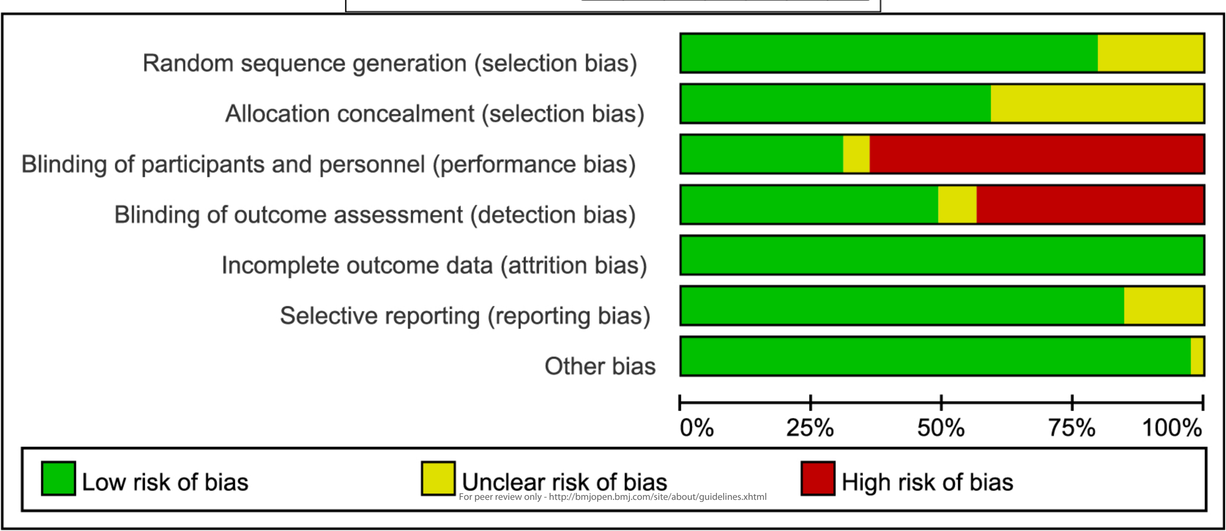

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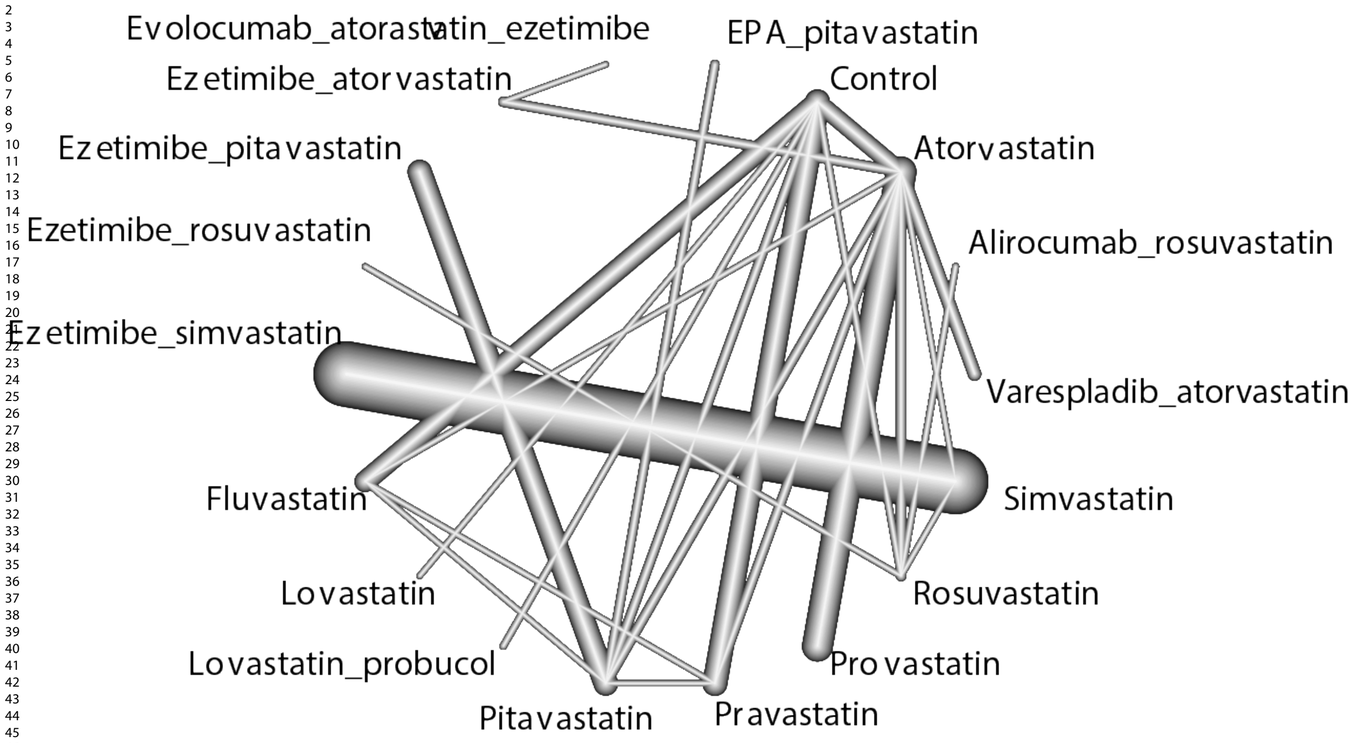

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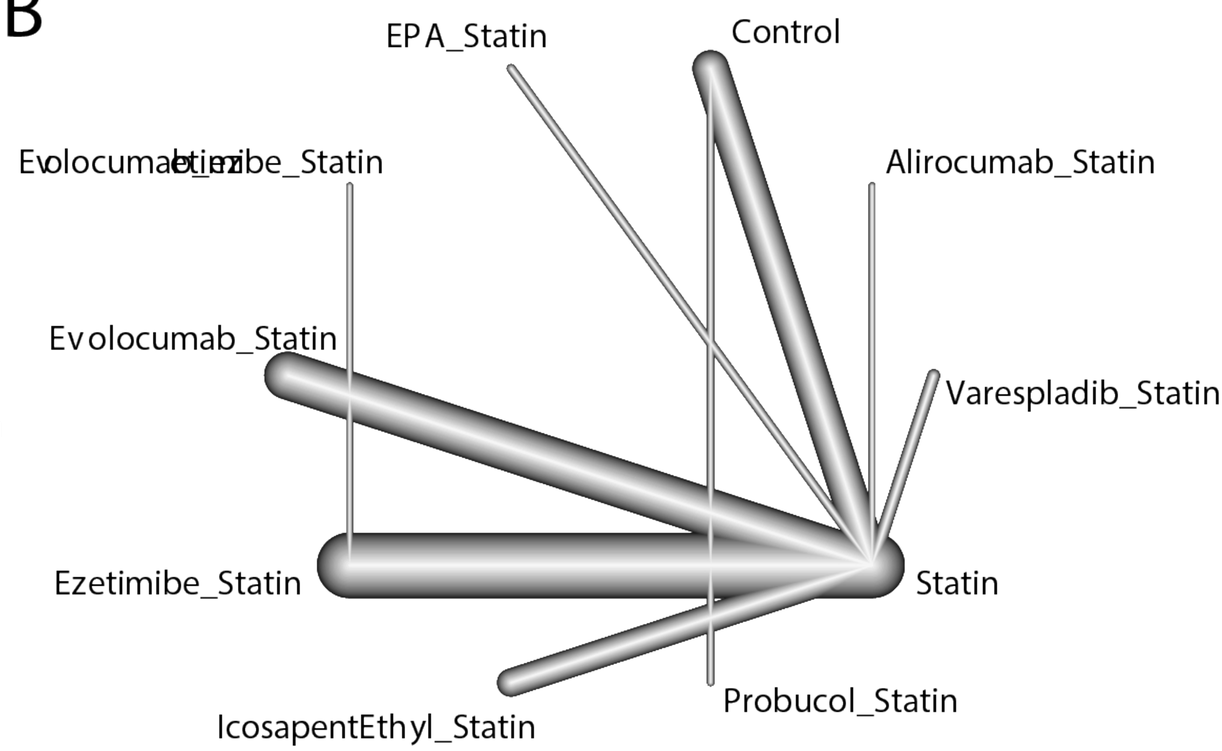

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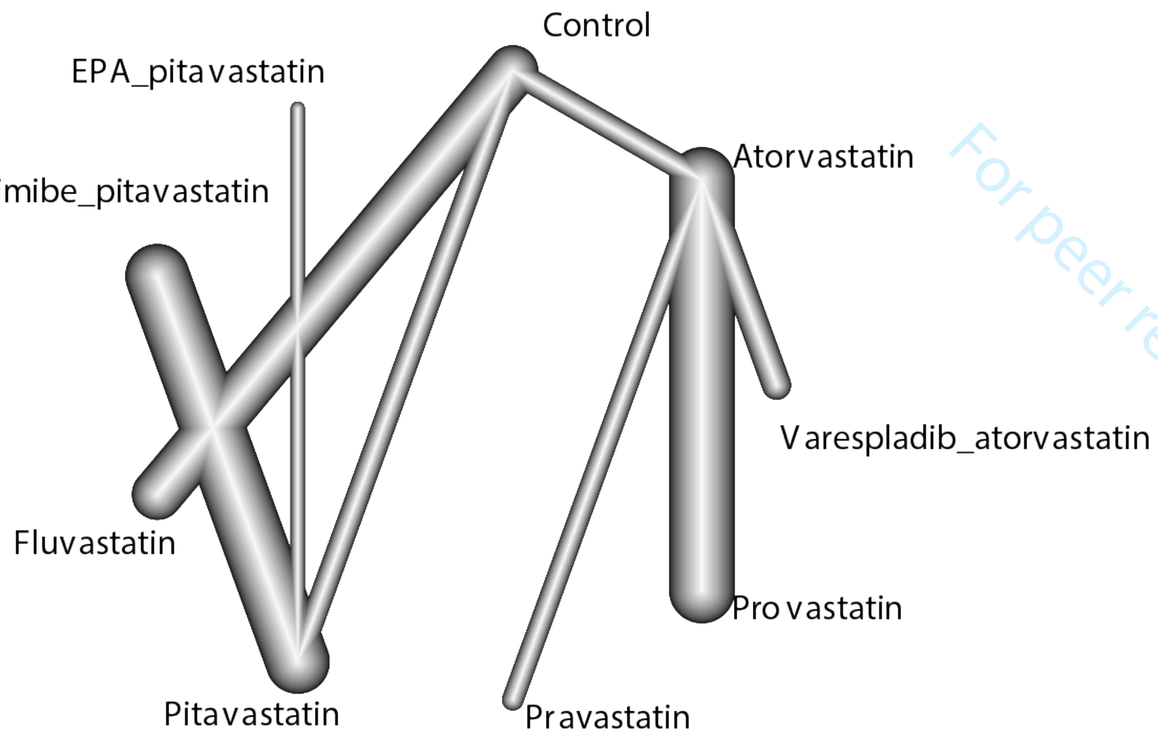

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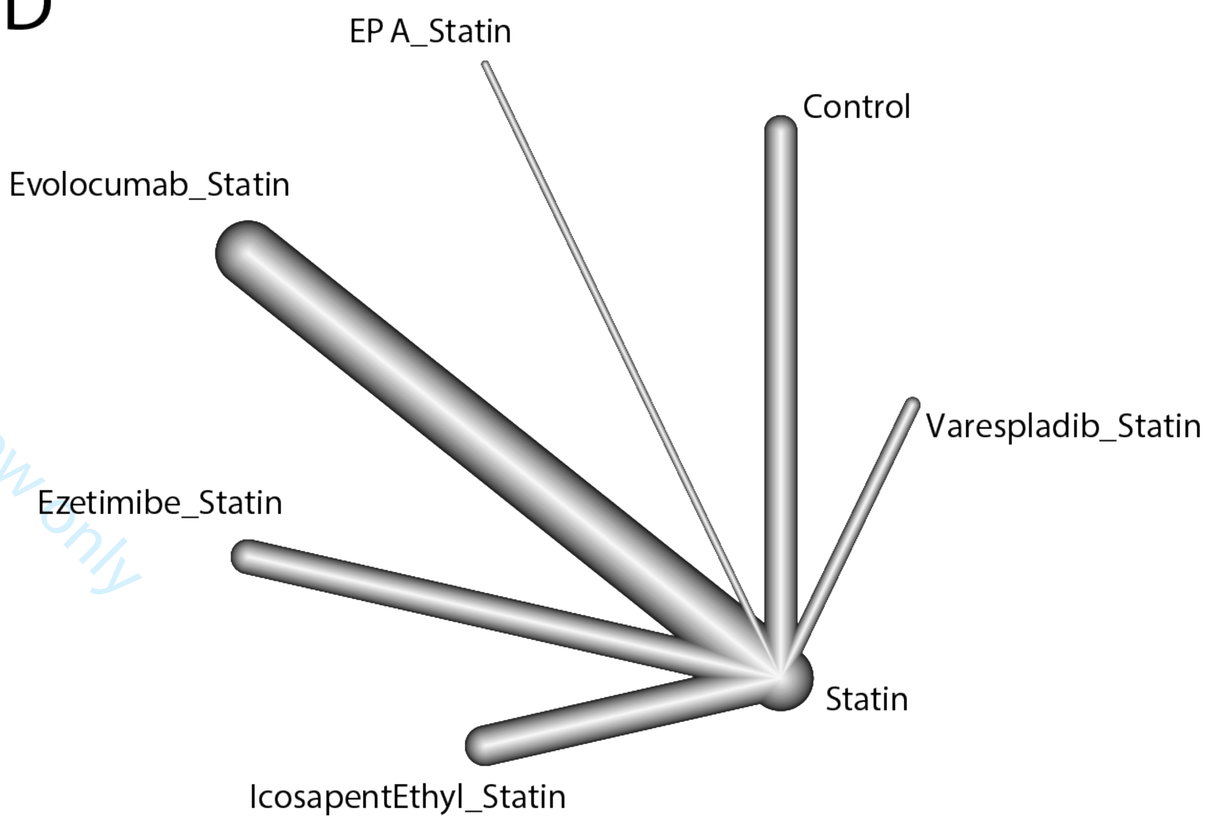

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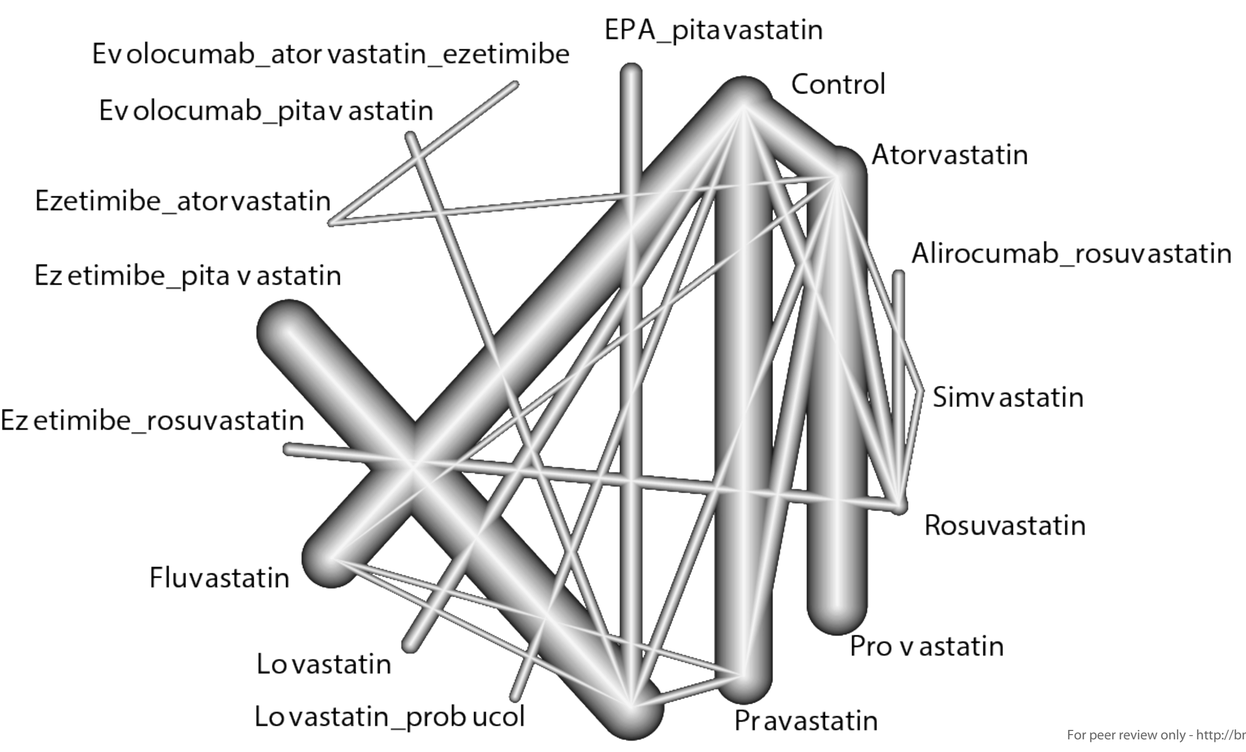

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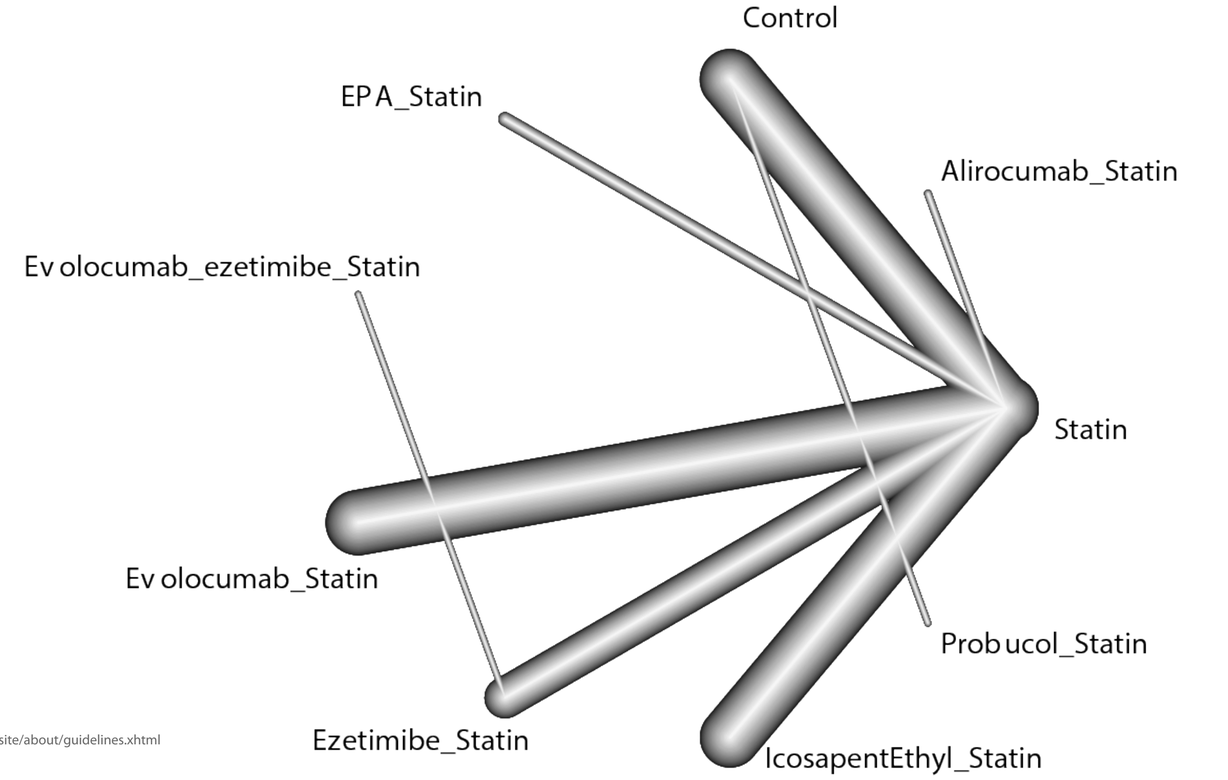

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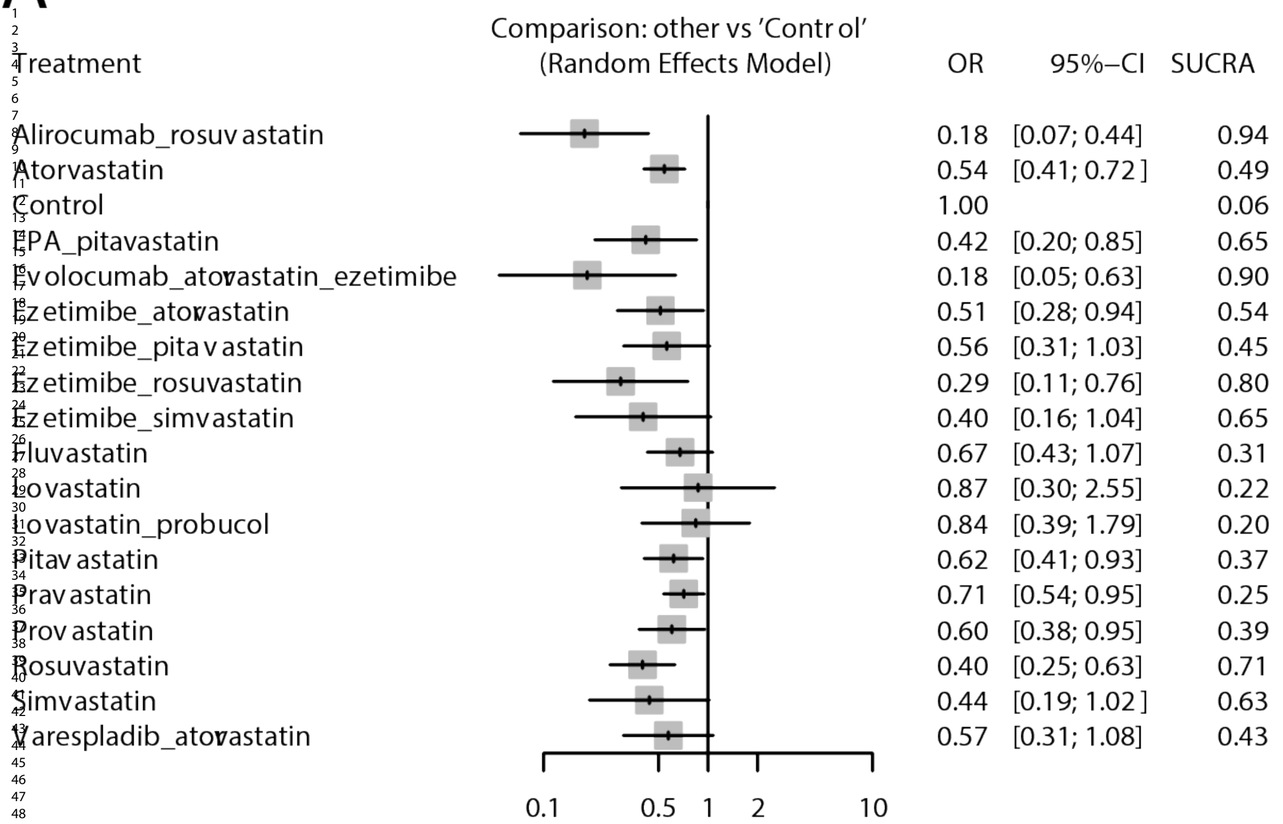

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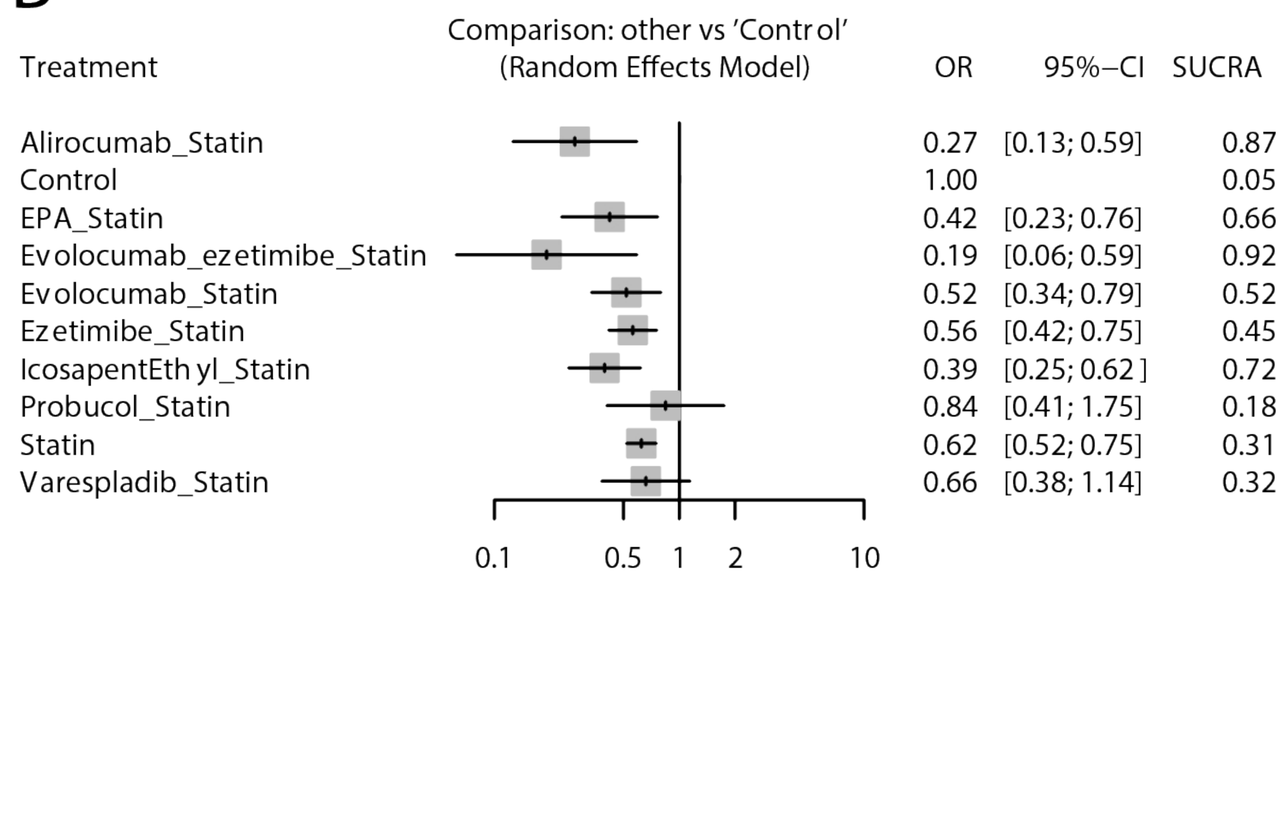

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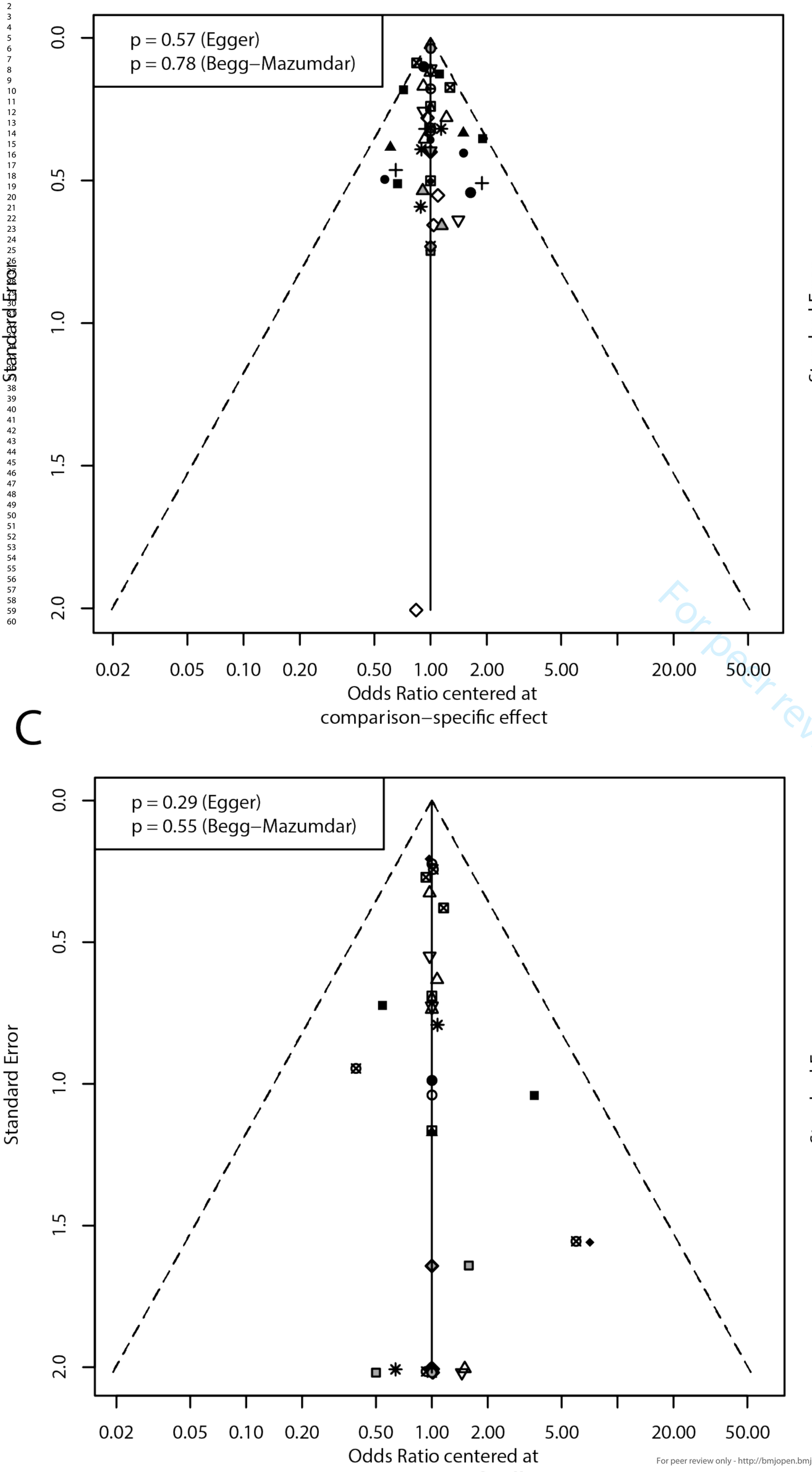

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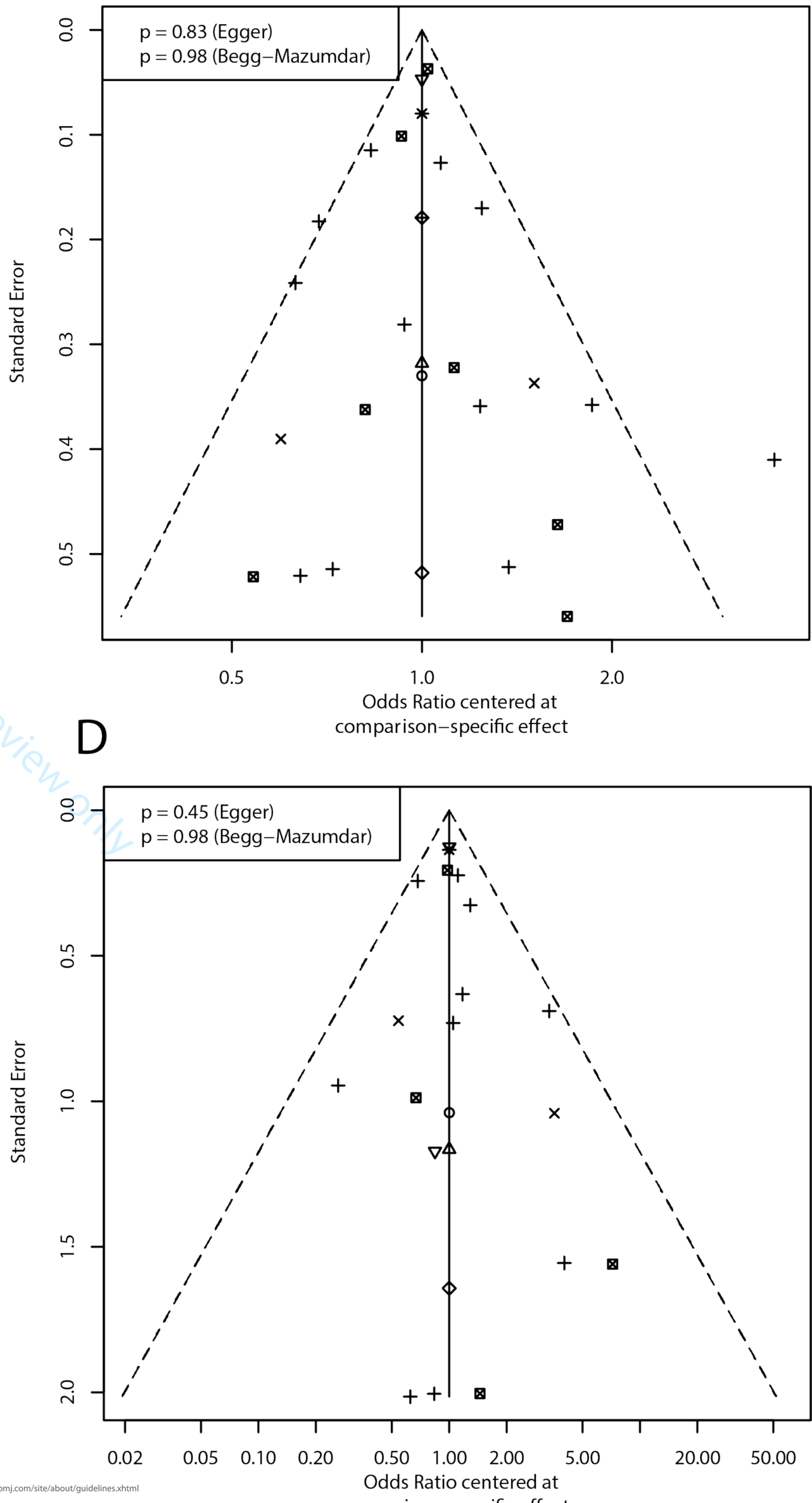

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1-4
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	11-41
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	16-17
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	20-23
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	24-31
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	19-22
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Figure1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	68-76
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	75-76
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	90-92
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	94-98
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	75-76
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	69-73
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	80-82
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	83-84
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	85-86
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	90-93
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	94-98
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	101-105
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	105-108
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	107-108

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	111-113
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	114-116
Study characteristics	17	Cite each included study and present its characteristics.	118-121
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	126-130
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	131-135
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	118-126
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	126-130
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	131-135
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	137-141
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	143-149
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	151-153
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	169-174
	23b	Discuss any limitations of the evidence included in the review.	176-179
	23c	Discuss any limitations of the review processes used.	181-184
	23d	Discuss implications of the results for practice, policy, and future research.	186-192
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	241-247
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	241-247
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	241-247
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	236
Competing interests	26	Declare any competing interests of review authors.	250
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	239

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

BMJ Open

Effectiveness of lipid-lowering therapy on mortality and major adverse cardiovascular event outcomes in patients undergoing percutaneous coronary intervention: a network meta-analysis of randomized controlled trials

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Effectiveness of lipid-lowering therapy on mortality and major adverse cardiovascular event outcomes in patients undergoing percutaneous coronary intervention: a network meta-analysis of randomized controlled trials

Chang-Jiang Deng[1], Ju Yan[2], Ying-Ying Zheng[1],Ting-Ting Wu[1], Ying Pan[1], Xian-Geng Hou[1],Si-Fan Wang1, Subinur·Sirajidin1, Mikereyi.Aimaitijiang1,Xiang Xie[1]

1. Department of Cardiology, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, 830011, P.R. China.
2. Department of Cardiology, Shaanxi Provincial People's Hospital, Xi'an, 710000, P.R. China.

Correspondence authors:

Xiang Xie, No. 137, Liyushan Road, Department of Cardiology, First Affiliated Hospital of Xinjiang Medical University, Urumqi, 830011 P.R., China. Tel: +8609914366168; Email: xiangxie999@sina.com

Abstract

Background

Emergency percutaneous coronary intervention (PCI) can quickly restore myocardial perfusion after acute coronary syndrome (ACS). Whether and which lipid-lowering regimens are effective in reducing major adverse cardiovascular events (MACEs) and mortality risk after PCI remain unclear.

Objective

This study will assess the benefits of different lipid-lowering regimens on the risk of MACEs and mortality in the post-PCI population by network meta-analysis.

Methods

Public literature databases, including PubMed, Embase, and the Cochrane Library, were searched from inception to August 2022. Randomized controlled trials (RCTs) on lipid-lowering regimens in post-PCI populations were included and analyzed. The outcomes were the incidence of all-cause mortality and MACE, whether reported as dichotomous or hazard ratio (HR) statistics.

Results

Thirty-nine RCTs were included. For MACEs, alirocumab plus rosuvastatin (OR: 0.18; 95% CI: 0.07-0.44;), evolocumab plus ezetimibe and statins (OR: 0.19; 95% CI:0.06-0.59), eicosapentaenoic acid (EPA) plus pitavastatin (HR: 0.67; 95% CI: 0.49-0.96), and icosapent ethyl plus statins (HR: 0.73; 95% CI: 0.62-0.86) had significant advantages and relatively high rankings. For mortality, rosuvastatin (OR: 0.30; 95% CI: 0.11-0.84), ezetimibe plus statins (OR: 0.55; 95% CI: 0.43-0.89) and icosapent ethyl plus statins (OR: 0.66; 95% CI: 0.45-0.96) had significant advantages compared to the control.

Conclusion

EPA, especially icosapent ethyl, plus statins had a beneficial effect on reducing the risk of MACEs and mortality in post-PCI patients. PCSK9i plus statins was able to reduce the risk of MACEs, but the risk of mortality remained unclear.

Key words:lipid-lowering therapy, major adverse cardiovascular events, mortality, network meta-analysis

Introduction

Acute coronary syndrome (ACS) is a term used to refer to a range of conditions associated with acute myocardial ischemia and/or infarction, which are usually due to coronary artery occlusion and acute ischemic necrosis of the myocardium due to progression of coronary atherosclerotic lesions(1-2).Emergency percutaneous coronary intervention (PCI) can quickly restore myocardial perfusion(3). Although the development of technological and procedural PCI have resulted in substantial improvements in clinical outcomes, recurrent coronary events may still occur after PCI(4).

The view of "residual cardiovascular risk" was introduced because MACE still occurs in some patients who received PCI during follow-up. PCI can treat focal manifestations of systemic progressive disease, but the residual risk of acute coronary syndrome is largely related to the systemic proatherosclerotic effect of poorly controlled cardiovascular risk factors(5). Lowering lipid levels, especially LDL-C, can halt the progression of coronary atherosclerosis and improve cardiovascular outcomes. Based on this view, it is believed that long-term optimal lipid-lowering therapy is effective in reducing long-term cardiovascular events after PCI. However, the view was still subject to challenges.

Based on data from the "Korea Acute Myocardial Infarction Registry", the proponents concluded that patients treated with statins had significantly lower rates of MACE, all-cause death, and cardiac death during the 2-year follow-up period after PCI application(6). However, a study of postoperative follow-up of PCI patients enrolled in the Melbourne Interventional Group registry concluded that statins have no significant benefit to MACEs after PCI(6). The controversy may be based on two reasons: on the one hand, is that the optimal lipid reduction target may not be achieved by using single statins(7,8). On the other hand, long-term high-dose application of statins increases the risk of intracerebral hemorrhage and other side effects(9,10).

There is a consensus on preloading high-dose statins to reduce MACEs in the perioperative period with PCI(11,12). However, there is still insufficient evidence for the continued application of lipid-lowering drugs to reduce the risk of long-term MACE and mortality. This study will assess the benefits of different lipid-lowering regimens on the risk of MACEs and mortality in the post-PCI population by network meta-analysis.

Methods

This study was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study was registered with PROSPERO (CRD 42018099600).

Patient and Public Involvement

None

Search strategy

Public literature databases, including PubMed, Embase, and the Cochrane Library, were searched from inception to August 2022 without language restrictions using the following search terms: (lipid-lowering or statin or simvastatin or rosuvastatin or atorvastatin or fluvastatin or lovastatin or pravastatin or pitavastatin or mevastatin or ezetimibe or “eicosapentaenoic acid” or “icosapent ethyl” or “bempedoic acid” or fibrate or bezafibrate or gemfibrozil or fenofibrate or ciprofibrate or evolocumab or alirocumab or evinocumab or volanesorsen or vupanorsen or pelacarsen or olezarsen or inclisiran or olpasiran) and (“percutaneous coronary intervention” or “coronary angioplasty”) and (random* or randomized or randomized). The references of relevant systematic reviews and meta-analyses were also searched to avoid omissions. The two authors conducted literature retrieval independently, and any conflicts were resolved through discussion with the third author.

Inclusion and exclusion criteria

The literature was included if it met the following criteria: 1, the study adopted a randomized controlled study design; 2, the study included patients who received PCI surgery or reported the subgroup of the population that received PCI; 3, the lipid-lowering regimen was applied to the population of the intervention group; 4, the

control group used a different lipid-lowering agent or regimen; and 5, the study reported the outcome of mortality and/or MACE. Exclusion criteria: 1, as preloading of statins before PCI had clear benefits, to determine whether application of lipid-lowering drugs after PCI also had beneficial effects. This work excluded the study on the preloading application of lipid-lowering drugs before PCI; 2, although high-dose lipid-lowering agents, such as statins, have a better lipid-lowering effect, long-term application may bring potential side effects(9-13). In this study, all agents were considered to be applied with reasonable doses, and dose–response studies were excluded. In addition, repeatedly published studies, protocols, conference abstracts, reviews, comments and editorials were also excluded.

Data extraction and quality assessment

Two authors independently extracted the information from the included studies. The contents include the name of the first author, publication year, study location, sample size (population received PCI), study abbreviation and registration number, lipid-lowering intervention and control, and follow-up time.

The outcomes analyzed were the incidence of all-cause mortality and MACE, whether reported as dichotomous or hazard ratio (HR) statistics based on Cox regression. The MACE outcome was selected to most closely approximate the composite endpoint, including mortality, MI, stroke, coronary revascularization, and restenosis. Study quality was assessed by two investigators using the Cochrane risk of bias assessment

tool, which included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential biases.

Statistical analysis

For each direct paired comparison, we used the odds ratios and their 95% confidence intervals (CIs) for dichotomous outcomes. The hazard ratios and their 95% CIs based on Cox regression results were also pooled for reporting. We conducted frequentist network meta-analysis (NMA) using random effect models with restricted maximum likelihood estimation to quantify network heterogeneity. The Q statistic was used to assess the sum of statistics for heterogeneity (within designs) and for overall inconsistency (between designs)(14). The ranking probabilities of each regimen were estimated using the surface under the cumulative ranking curve (SUCRA), and a comparison-adjusted funnel plot was used to examine potential publication biases in NMA. P values of less than 0.05 were considered to be statistically significant. The NMA was performed using R language with the "netmeta" package.

Results

After removing duplications, we obtained 1588 literature items. After a screen of the titles and abstracts, 1515 irrelevant studies were excluded. Seventy-three articles were screened for full text. The following articles were excluded: dose–response studies (8), no PCI population or subgroup was reported (6); no mortality or MACE-related

outcomes were reported (6); repeated publication (5); study related to preloading of lipid-lowering agents (4); study not related to lipid-lowering agents (3); protocol (1); non-RCT design (1). Finally, 39 articles were included containing 54478 patients after PCI(15-53) (Figure 1).

Among the included studies, the publication period ranged from 1991 to 2022. The research locations were mainly in Asia (China, Japan and South Korea), Europe (Netherlands, France, and Italy), America, and multiple centers. There were 10 studies with sample sizes greater than 1000 patients. There were also 22 studies with publicly available clinical study registration numbers (Table 1). In terms of design quality, all included studies were RCTs. Therefore, the design quality is generally high. The main factors potentially affecting design quality were the blinding of participants and personnel and blinding of outcome assessment (Figure 2). However, as the desired outcomes were mortality and MACE, the subjective factors of the investigator had little influence on the outcomes.

Table 1. The characteristics of included studies

Study	Location	Sample size	Abbreviation	Register ID	Intervention	Control	Follow-up#
Lorenz Räber 2022 [15]	European	300	PACMAN-AMI	NCT03067844	Alirocumab;rosuvastatin	Placebo;rosuvastatin	52W
Peterson, B. E. 2022 [16]	Multicenter	3408	REDUCE-IT PCI	NCT01492361	Icosapent ethyl;statins	Placebo;statins	4.8Y
Remo H.M. Furtado 2022 [17]	Multicenter	17073	FOURIER	NCT01764633	Evolocumab;statins	Placebo;statins	2.2Y
Tomoaki Okada 2022 [18]	Japan	102	-	UMIN000028729	Evolocumab;pitavastatin	Pitavastatin	4W
Yan Hao 2022 [19]	China	136	-	-	Evolocumab;atorvastatin;ezetimibe	Ezetimibe;atorvastatin	3M
Deng YF 2021 [20]	China	90	-	-	Ezetimibe;atorvastatin	Atorvastatin	1Y

Sun C 2021 [21]	China	171	-	ChiCTR-IPR-17012219	Ezetimibe;rosuvastatin	Rosuvastatin	3M
Weifeng He 2020 [22]	China	192	-	-	Atorvastatin vs. Rosuvastatin vs. Simvastatin	-	6M
Kiyoshi Hibi 2018 [23]	Japan	128	Ezetimibe-ACS	NCT00549926	Ezetimibe;pitavastatin	Pitavastatin	1Y
Eui Im 2017 [24]	Korea	2000		NCT01557075	Atorvastatin	Pravastatin	1Y
Hagiwara N 2017 [25]	Japan	1734	HIJ-PROPER	UMIN000002742	Ezetimibe;pitavastatin	Pitavastatin	36M
J Guo 2017 [26]	China	137	-	-	Rosuvastatin	Control	1Y
Wang YB 2017 [27]	China	132	-	ChiCTR-IPR-15007035	Pitavastatin	Atorvastatin	6M
Watanabe T 2017 [28]	Japan	193	CHERRY	UMIN000002815	EPA;pitavastatin	Pitavastatin	6-8M
Zhi Liu 2017 [29]	China	102	-	-	Ezetimibe;atorvastatin	atorvastatin 20mg/d	1Y
Kazumasa Nosaka 2016 [30]	Japan	241	-	UMIN000016723	EPA;pitavastatin	Pitavastatin	1Y
Kensuke Matsushita 2016 [31]	Japan	118	Yokohama-ACS	NCT00549926	Atorvastatin vs. Pitavastatin vs. Pravastatin vs. Fluvastatin	-	10.3M
Christopher P Cannon 2015 [32]	Multicenter	12941	IMPROVE-IT	NCT00202878	Ezetimibe;simvastatin	Simvastatin	6M
Kenichi Tsujita 2015 [33]	Multicenter	246	PRECISE-IVUS	NCT01043380	Ezetimibe;atorvastatin	Atorvastatin	1Y
Stephen J. Nicholls 2015 [34]	Multicenter	3295	VISTA-16	NCT01130246	Varespladib;atorvastatin	Placebo;atorvastatin	6M
Zhang JR 2015 [35]	China	104	-	-	Atorvastatin	Rosuvastatin	6M
Mario Leoncin 2014 [36]	Italy	333	PRATO-ACS	NCT01185938	Rosuvastatin	Control	6M
Hiroyuki Takano 2013 [37]	Japan	458	PEARL	UMINC000000428	Pitavastatin	Control	35.5M
Tsuyoshi Nozue 2013 [38]	Japan	164	TRUTH	UMIN000004627	Pitavastatin	Pravastatin	2Y
Jean-Marc Lablanche 2010 [39]	Multicenter	887	CENTAURUS	NCT00296387	Rosuvastatin	Atorvastatin	3M
C. Michael Gibson 2009 [40]	US	2868	PROVE IT-TIMI 22	NCT00382460	Atorvastatin	Provastatin	2Y
Han Yaling 2009 [41]	China	1275	-	NCT00405717	Atorvastatin	Provastatin	1Y
Takafumi Hiro 2009 [42]	Japan	307	JAPAN-ACS	NCT00242944	Pitavastatin	Atorvastatin	1Y
Tomotaka Dohi 2009 [43]	Japan	180	Extended-ESTABLISH trial	-	Atorvastatin	Control	4Y
Toru Toi 2009 [44]	Japan	160	-	-	Pitavastatin	Atorvastatin	17D
Xu Kai 2007 [45]	China	648	-	-	Atorvastatin	Control	2Y
Bae JH 2004 [46]	Korea	205	-	-	Atorvastatin	Control	6M
Patrick W J C Serruys 2002 [47]	Multicenter	1677	LIPS	-	Fluvastatin	Placebo	3.9Y
Han J.G.H. Mulder 2000 [48]	Netherland	201	REGRESS	-	Pravastatin	Placebo	2Y
Greg C. Flaker 1999 [49]	Multicenter	1154	CARE trial	-	Pravastatin	Placebo	6Y

MICHEL E. BERTRAND 1997 [50]	France	695	PREDICT	-	Pravastatin	Placebo	6M
J H O'Keefe Jr 1996 [51]	US	200	APPLE	-	Probucol;lovastatin	Placebo	6M
Haruhiko Onaka 1994 [52]	Japan	66	-	-	Pravastatin	Control	5M
Rakesh Sahni 1991 [53]	US	157	-	-	Lovastatin	Control	6M

Abbreviations: EPA: eicosapentaenoic acid.

#: Follow-up period: Y: years; M: months; W: weeks; D: days

As two studies did not specify the types of statins, the network meta-analysis will be divided into two parts. One part was analyzed based on specific types of statins, and the other was based on taking statins as a whole. For the dichotomous results of MACE, the NMA based on specific types of statins included 18 lipid-lowering regimens. The Q test for heterogeneity was p = 0.07, and for inconsistency, it was p = 0.16, indicating no evidence for heterogeneity and inconsistency in the NMA.

In pairwise comparisons with the control, alirocumab plus rosuvastatin (OR: 0.18; 95% CI: 0.07-0.44; SUCRA: 0.94), evolutionab plus atorvastatin and ezetimibe (OR: 0.18; 95% CI: 0.05-0.63; SUCRA: 0.90), ezetimibe plus rosuvastatin (OR: 0.29; 95% CI: 0.11-0.76; SUCRA: 0.80) have significant advantages and relatively high SUCRA rankings. No potential publication bias was found according to the comparison-adjusted funnel plot (Figure 3).

In the NMA based on taking statins as a whole, ten regimens were analyzed. Evolocumab plus ezetimibe and statins (OR: 0.19; 95% CI: 0.06-0.59; SUCRA: 0.92), alirocumab plus statins (OR: 0.27; 95% CI: 0.13-0.59; SUCRA: 0.87), and coscapent

ethyl plus statins (OR: 0.39; 95% CI: 0.25-0.62; SUCRA: 0.72) have significant advantages and relatively high SUCRA rankings. No potential publication bias was found.

For the HR results of MACEs, the NMA based on specific types of statins included nine regimens. The Q test for heterogeneity was p = 0.964 and because the network comparisons lack loops. Therefore, the results were considered consistent. Compared to the control, eicosapentaenoic acid (EPA) plus pitavastatin (HR: 0.67; 95% CI: 0.49-0.96; SUCRA: 0.91), atorvastatin (HR: 0.76; 95% CI: 0.63-0.90; SUCRA: 0.83), and varespladib plus atorvastatin (HR: 0.77; 95% CI: 0.61-0.97; SUCRA: 0.77) have significant advantages and relatively high SUCRA rankings. Potential publication bias was not analyzed due to a smaller number of included studies.

In the NMA based on taking statins as a whole, seven regimens were analyzed. EPA plus statins (HR: 0.60; 95% CI: 0.42-0.85; SUCRA: 0.96) and icosapent ethyl plus statins (HR: 0.73; 95% CI: 0.62-0.86; SUCRA: 0.81) had significant advantages over the control.

For the dichotomous results of mortality, the NMA based on specific types of statins included 17 lipid-lowering regimens. The Q test for heterogeneity was p = 0.78, and for inconsistency, it was p = 0.99. Due to the rare occurrence of events, the results of the comparison were low precision with a large standard error. Compared to the

control, only rosuvastatin (OR: 0.30; 95% CI: 0.11-0.84; SUCRA: 0.79) showed a significantly better effect. Ezetimibe plus rosuvastatin had a relatively high SUCRA ranking, but there was no significant difference compared to the control (OR: 0.14; 95% CI: 0.02-1.26; SUCRA: 0.86). No potential publication bias was found (Figure 4).

In the NMA based on taking statins as a whole, nine regimens were analyzed. Ezetimibe plus statins (OR: 0.55; 95% CI: 0.43-0.89; SUCRA: 0.75) and icosapent ethyl plus statins (OR: 0.66; 95% CI: 0.45-0.96; SUCRA: 0.63) had significant advantages compared with the blank control group. No potential publication bias existed. NMA analysis was not performed due to the small number of studies reporting HR for mortality (Figure 5).

Discussion

This study analyzed the benefits of lipid-lowering therapy on mortality and MACE outcomes in patients who received PCI by network meta-analysis. The results showed that several lipid-lowering regimens could reduce the risk of MACEs compared with the blank control. Icosapent ethyl plus statins had the benefit of reducing both the risk of MACEs and mortality. However, EPA plus statins had more advantages in reducing the risk of MACEs. Of note, based on the current evidence, alirocumab and evolocumab plus statins had obvious advantages in reducing the risk of MACEs but had no obvious benefit in reducing the risk of mortality.

EPA is a long-chain omega-3 polyunsaturated fatty acid. Long-term intake of EPA can reduce the residual cardiovascular risk to reduce the risk of MACEs(54). In terms of pathological mechanisms, EPA combined with pitavastatin can reduce the lipid volume of coronary artery plaque and total atherosclerotic plaque volume in patients who receive PCI, which may be the reason for the reduced risk of MACEs(55).

Icosapent ethyl is a highly purified and stable eicosapentaenoic acid ethyl ester that has potential higher anti-inflammatory, antioxidant, plaque stability and cell membrane stability effects(56). In the NMA results, icosapent ethyl plus statins had significant benefits for either mortality or MACEs in patients who received PCI, which was an ideal regimen for the population.

Ezetimibe inhibits the absorption of cholesterol and has a synergistic lipid-lowering pharmacological effect with statins to further reduce the risk of death and MACE. In particular, when combined with rosuvastatin, it has a stronger lipid-lowering effect with a high safety profile without the risk of drug interactions(57). Our NMA results also showed that it can reduce the risk of MACE and mortality. According to the guidelines for the management of dyslipidemia from the European Society of Cardiology and the European Atherosclerosis Society, ezetimibe was recommended if the LDL-C level was not reached(58,59). The American College of Cardiology guidelines also recommend adding ezetimibe when using maximally tolerated statin

therapy and if LDL-C levels remain ≥ 70 mg/dL(60). These benefits have also been demonstrated in the secondary prevention of PCI.

Alirocumab and evolumab are both proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), which can increase the level of LDL receptor in the liver, thus improving the ability of the liver to bind LDL-C and reducing the level of peripheral LDL-C(61). There was also a synergistic lipid-lowering pharmacological effect when PCSK9i was combined with statins that significantly reduced LDL-C and atherosclerosis event risk; however, there was still controversy regarding the mortality risk reduction(62). It has been suggested that the powerful effect of PCSK9I on reducing LDL-C predisposes patients to hypocholesterolemia, which will not increase the risk of cerebral hemorrhage ,PCSK9i may be a preferred lipid-lowering agent in patients with elevated ICH risk(63,64). On the other hand, PCSK9i could not reduce serum inflammatory factors, suggesting that it may not reduce the risk of residual inflammation in the post-PCI population(65).

In the results of this study, lipid-lowering therapy strategies had general advantages in reducing MACE risk. However, for all-cause mortality, the advantage of lipid-lowering therapy was not obvious. Based on dichotomous outcomes of mortality, some strategies may even have a tendency to increase the mortality risk. This challenges the opinion that lipid-lowering therapy is recommended after PCI(66). A large sample size retrospective study suggests that statins can reduce the risk of all-

cause death in patients with coronary artery disease undergoing PCI, regardless of personal cholesterol levels(67). Alternatively, the “Lipid Paradox” view has been proposed and indicated that higher levels of LDL-C and triglycerides on admission are associated with better clinical outcomes. Especially in patients with ST-elevation myocardial infarction, lower LDL-C levels were associated with worse mortality outcomes(68). However, this view is also controversial(69).

On the other hand, it is possible that the contribution of LDL-C reduction to the risk of mortality outcomes is obscured by the other confounding factors. For example, inflammatory status may also have an important impact on patient mortality risk. In a cohort of post-PCI patients with low LDL-C levels, residual inflammatory risk also had a significant effect on overall mortality(70). C-reactive protein can also predict long-term mortality in post-PCI patients independent of LDL-C levels(71). In addition, cardiac remodeling also has an important impact on the survival outcome of people after PCI(72).

There are still several limitations in this study. First, this study was based on the study level instead of the individual level, making it difficult to consider the individual confounding factors in the analysis. Second, two included studies did not specify the type of statins, so our study had to be analyzed separately according to whether all statins were considered as a whole. Third, the criteria for defining MACEs varied among studies that contributed to heterogeneity among the study results. Fourth, many included studies reported only dichotomous outcomes but did not report the HR

results, resulting in the incompleteness of the relevant analysis results.

In conclusion, the results of this study suggest that EPA, especially icosapent ethyl, plus statins had a beneficial effect on reducing the risk of MACEs and mortality in post-PCI patients. PCSK9i plus statins was able to reduce the risk of MACEs, but the risk of mortality remained unclear.

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Author contributions

Chang-Jiang Deng completed the manuscript, Ju Yan, Ting-Ting Wu,Ying Pan,Ying-Ying Zheng guided the data analysis and the production of the figures, Xian-Geng Hou,Si-Fan Wang, Subinur·Sirajidin, Mikereyi.Aimaitijiang,Xiang Xie read and approved the fnal manuscript.

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Declarations

Ethics approval and consent to participate

This study does not involve human participants and ethical approval was not required.

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not applicable.

Competing interests

The authors declare that they have no competing interests.

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[dataset]72.Abbate A, Biondi-Zoccai GG, Appleton DL, Erne P, Schoenenberger AW, Lipinski MJ, Agostoni P, Sheiban I, Vetrovec GW (2008) Survival and cardiac remodeling benefits in patients undergoing late percutaneous coronary intervention of the infarct-related artery: evidence from a meta-analysis of randomized controlled

trials. J Am Coll Cardiol 51(9):956-64.

Figure 1. Flowchart of the study selection process for eligible studies

Figure 2. Methodological quality assessment of included studies

Figure 3. Network plots of comparisons for major outcomes included in the analyses. A: dichotomous results of MACE based on specific types of statins; B: dichotomous results of MACE based on taking statins as a whole; C: hazard ratio results of MACE based on specific types of statins; D: hazard ratio results of MACE based on taking statins as a whole; E: dichotomous results of mortality based on specific types of statins; F: dichotomous results of mortality based on taking statins as a whole.

Figure 4. Forest plots of lipid-lowering therapy compare to control for outcomes in network meta-analysis with SUCRA ranking results. A: dichotomous results of MACE based on specific types of statins; B: dichotomous results of MACE based on taking statins as a whole; C: hazard ratio results of MACE based on specific types of statins; D: hazard ratio results of MACE based on taking statins as a whole; E: dichotomous results of mortality based on specific types of statins; F: dichotomous results of mortality based on taking statins as a whole.

Figure 5. The comparison-adjusted funnel plot for assessing all main outcomes. A: dichotomous results of MACE based on specific types of statins; B: dichotomous results of MACE based on taking statins as a whole; C: dichotomous results of mortality based on specific types of statins; D: dichotomous results of mortality based on taking statins as a whole.

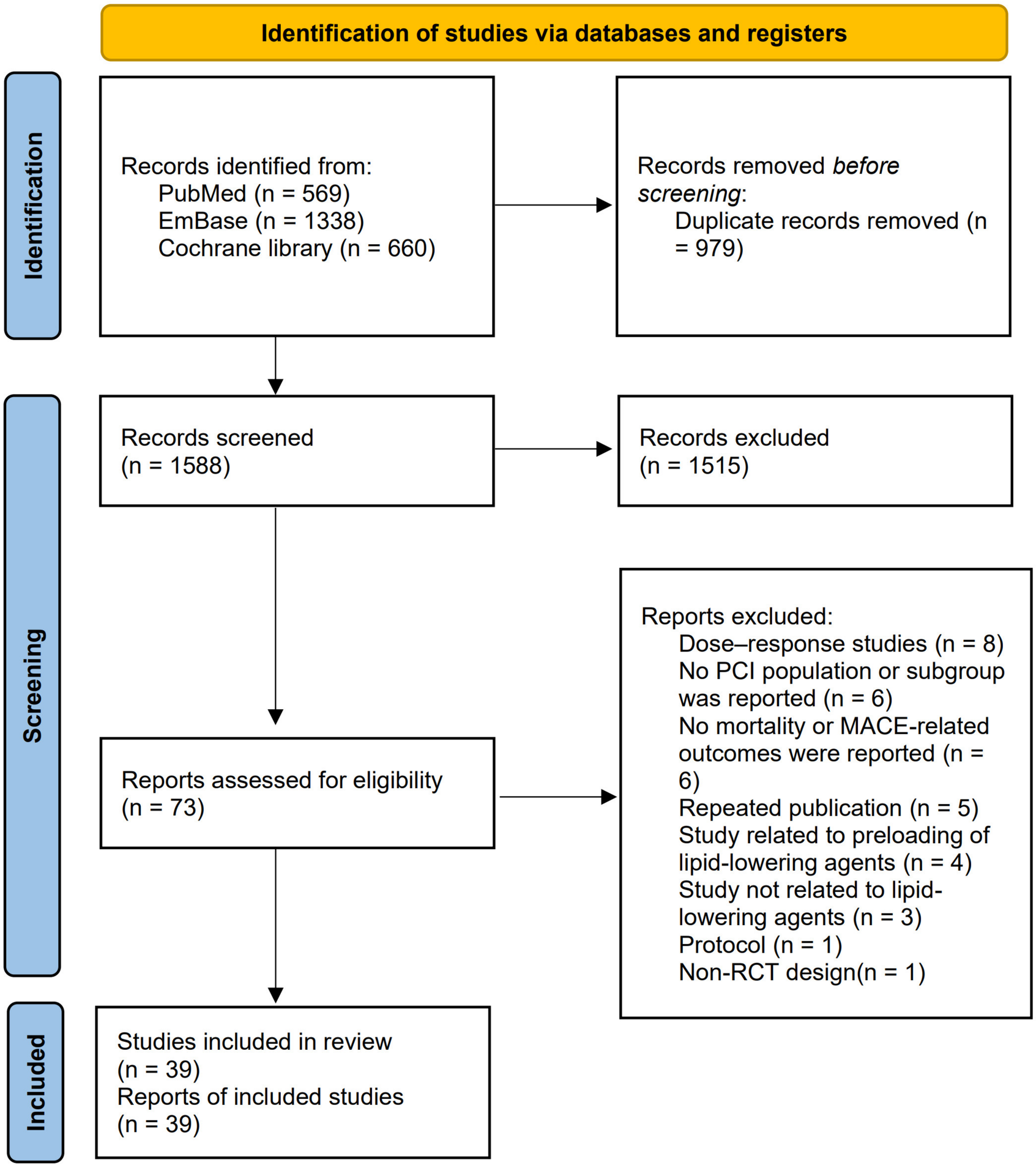
Authors and Afliations

Chang-Jiang Deng, Ju Yan, Ying-Ying Zheng,Ting-Ting Wu, Ying Pan, Xian-Geng Hou,Si-Fan Wang, Subinur·Sirajidin, Mikereyi·Sirajidin,Xiang Xie

Chang-Jiang Deng	Xian-Geng Hou
1187229853@qq.com	380138554@qq.com
Ju Yan	Si-Fan Wang
yyjj2017@163.com	562654119@qq.com
Ying-Ying Zheng	Subinur·Sirajidin
zhengying527@163.com	496568064@qq.com
Ting-TingWu	Mikereyi·Aimaitijiang
1255723526@qq.com	3195676352@qq.com
Ying Pan	Xiang Xie
2475854195@qq.com	xiangxie999@sina.com

Department of Cardiology, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, 830011, P.R. China.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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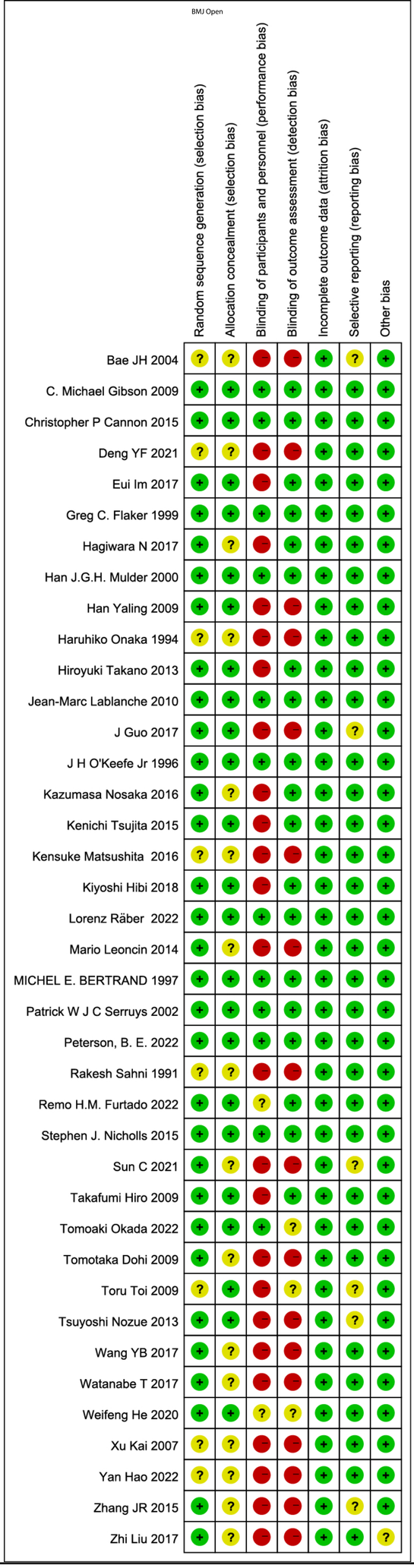
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Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Bae JH 2004
C. Michael Gibson 2009
Christopher P Cannon 2015
Deng YF 2021
Eui Im 2017
Greg C. Flaker 1999
Hagiwara N 2017
Han J.G.H. Mulder 2000
Han Yaling 2009
Haruhiko Onaka 1994
Hiroyuki Takano 2013
Jean-Marc Lablanche 2010
J Guo 2017
J H O'Keefe Jr 1996
Kazumasa Nosaka 2016
Kenichi Tsujita 2015
Kensuke Matsushita 2016
Kiyoshi Hibi 2018
Lorenz Räber 2022
Mario Leoncin 2014
MICHEL E. BERTRAND 1997
Patrick W J C Serruys 2002
Peterson, B. E. 2022
Rakesh Sahni 1991
Remo H.M. Furtado 2022
Stephen J. Nicholls 2015
Sun C 2021
Takafumi Hiro 2009
Tomoaki Okada 2022
Tomotaka Dohi 2009
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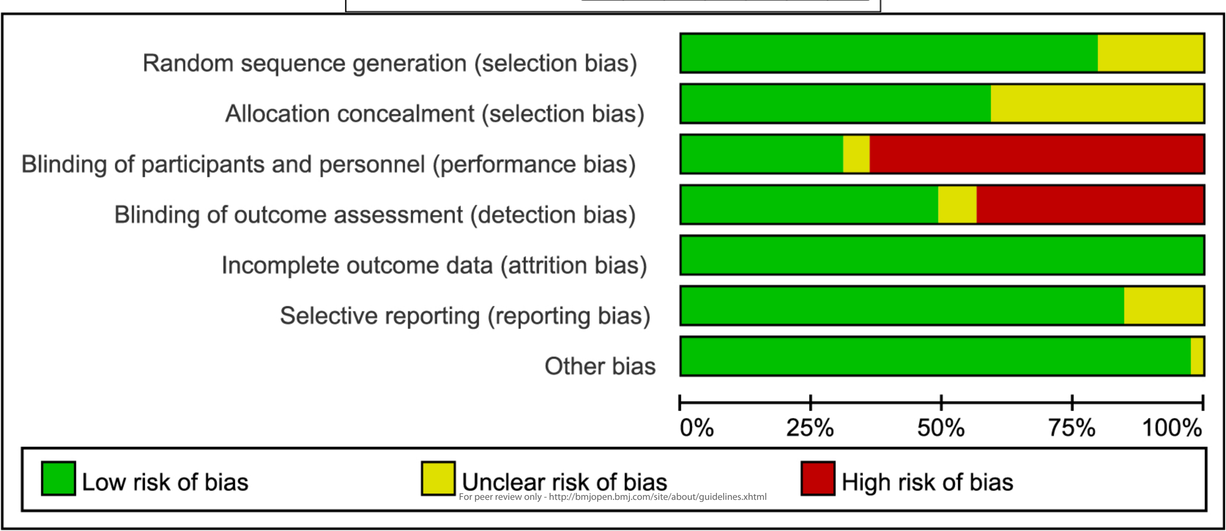
Tsuyoshi Nozue 2013
Wang YB 2017
Watanabe T 2017
Weifeng He 2020
Xu Kai 2007
Yan Hao 2022
Zhang JR 2015
Zhi Liu 2017


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
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100%
Low risk of bias
Unclear risk of bias
High risk of bias

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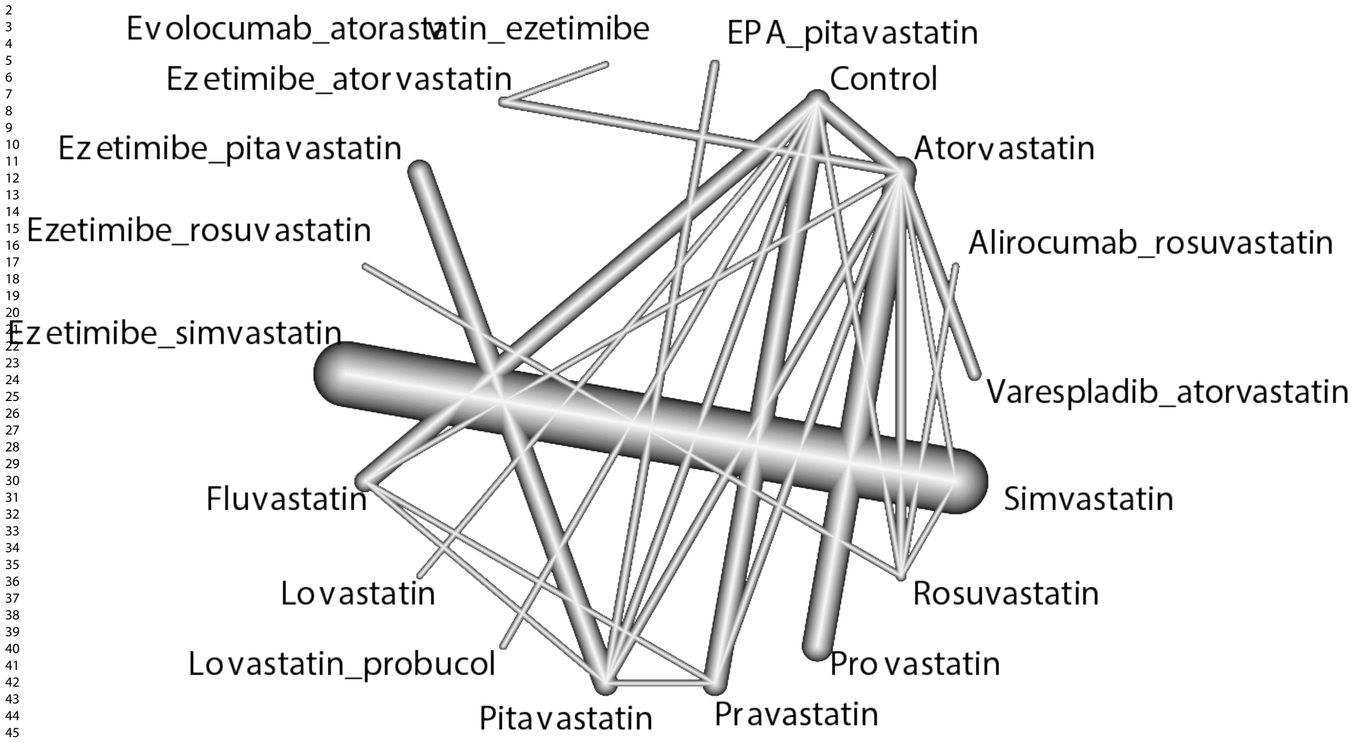

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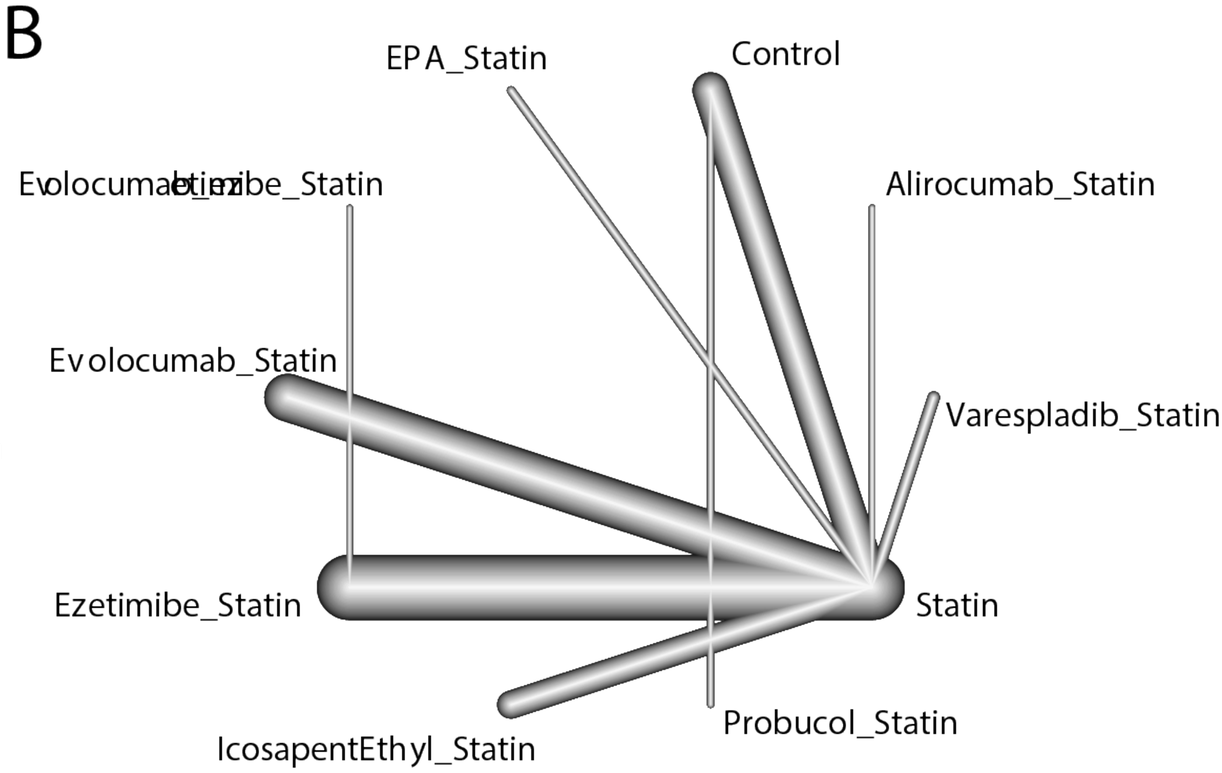

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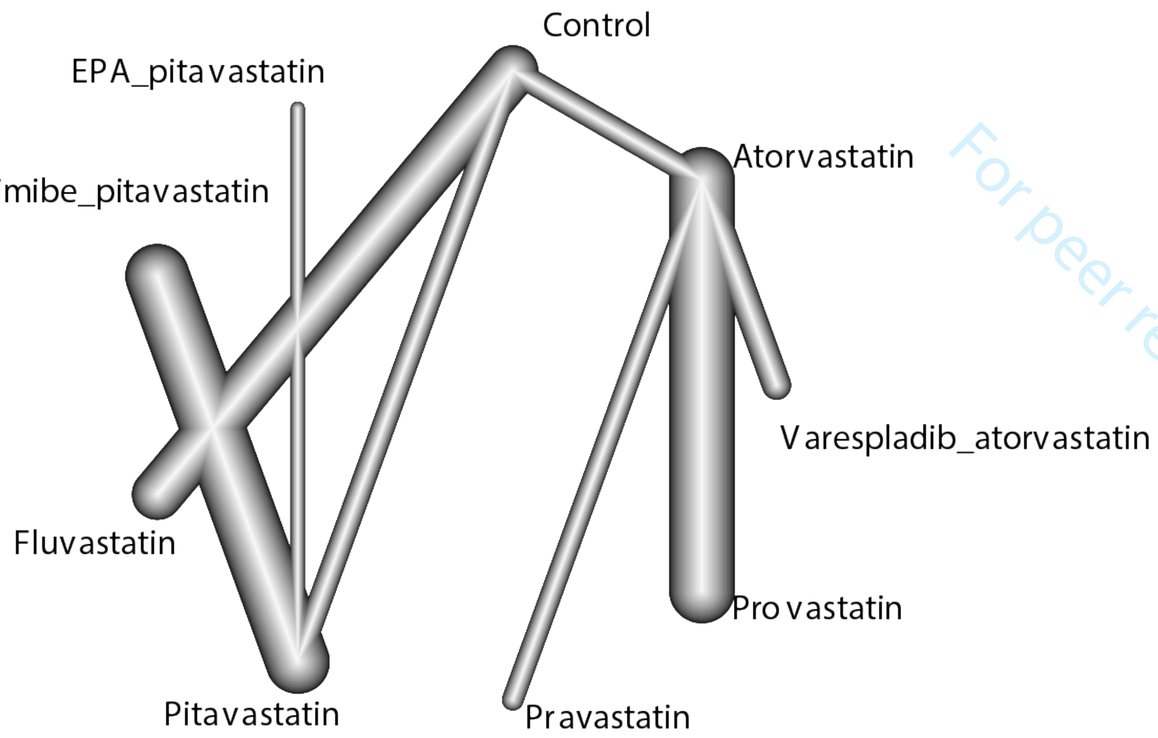

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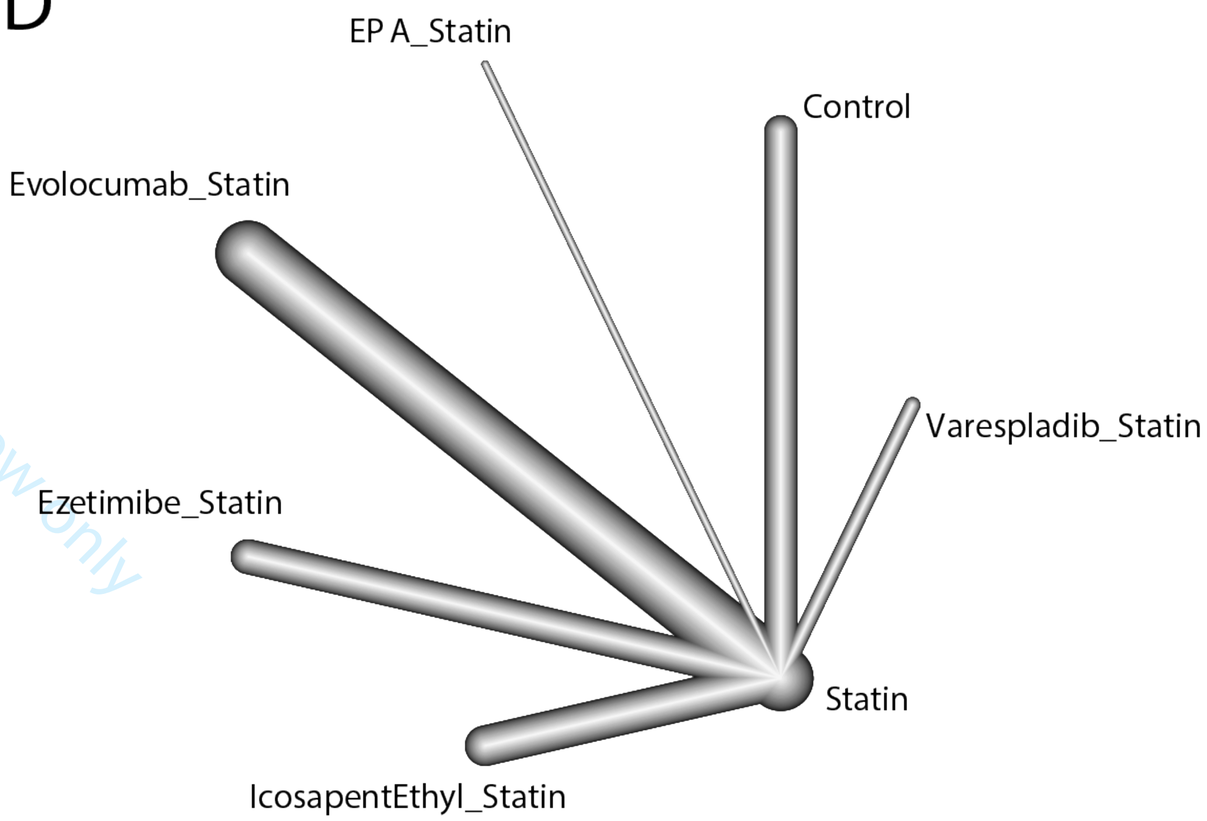

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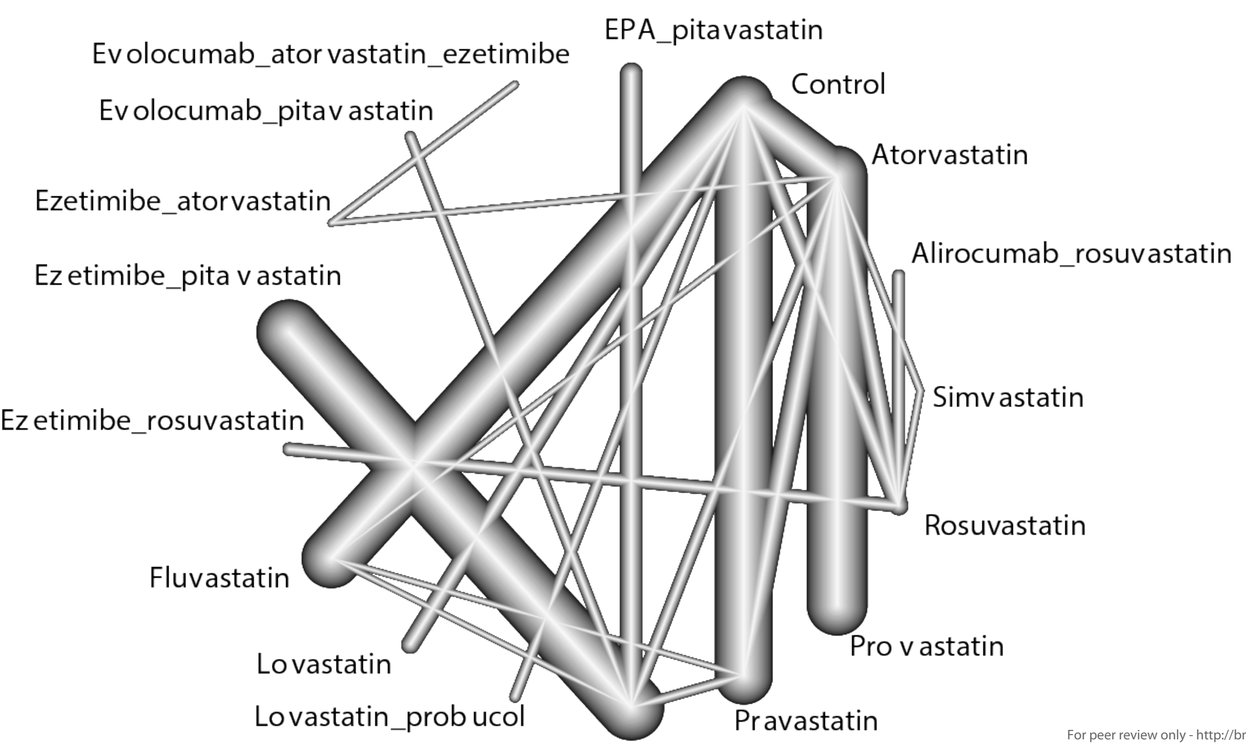

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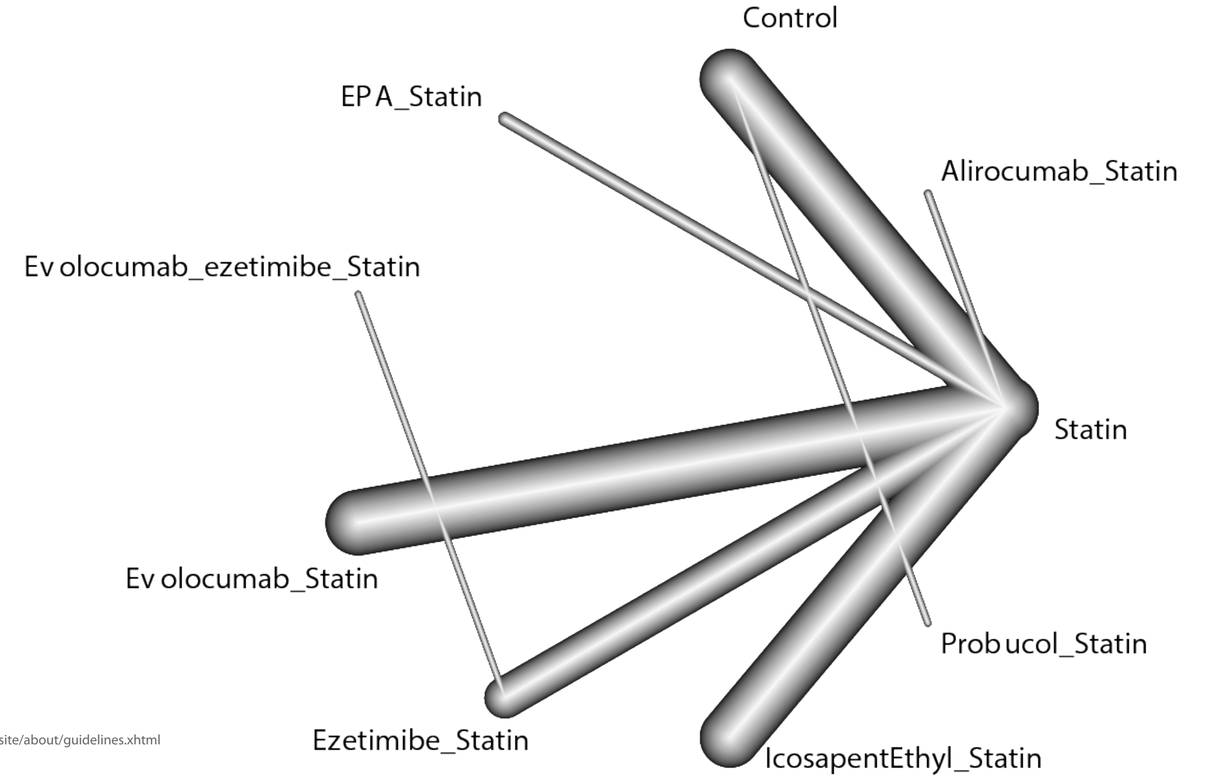

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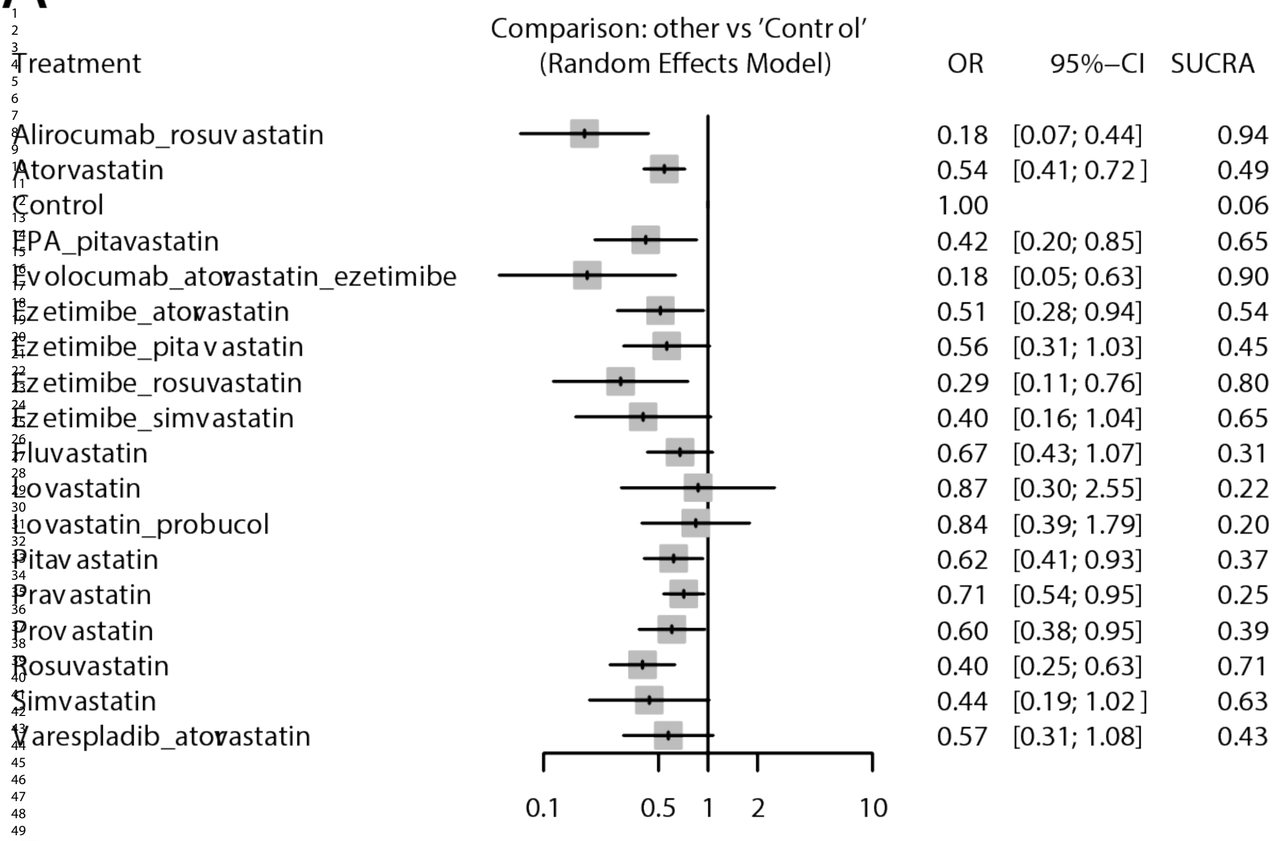

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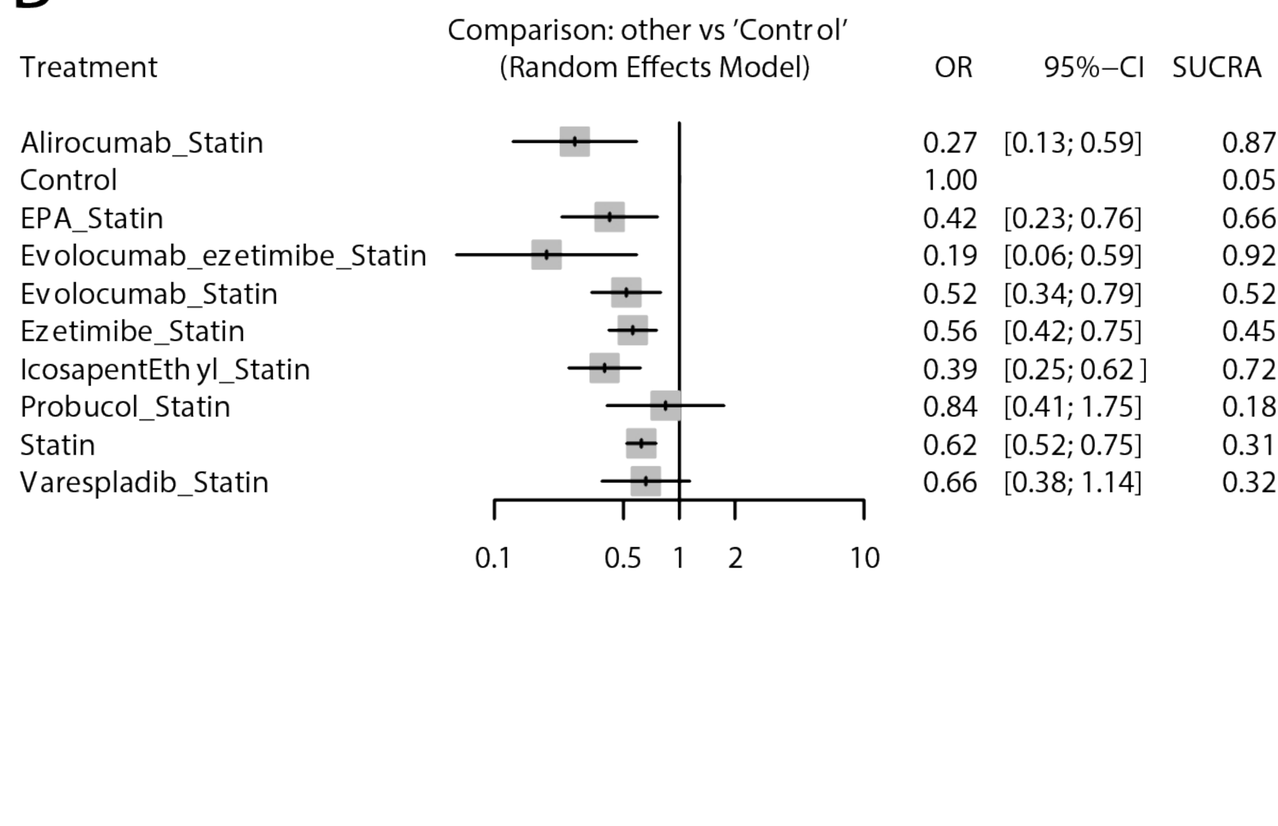

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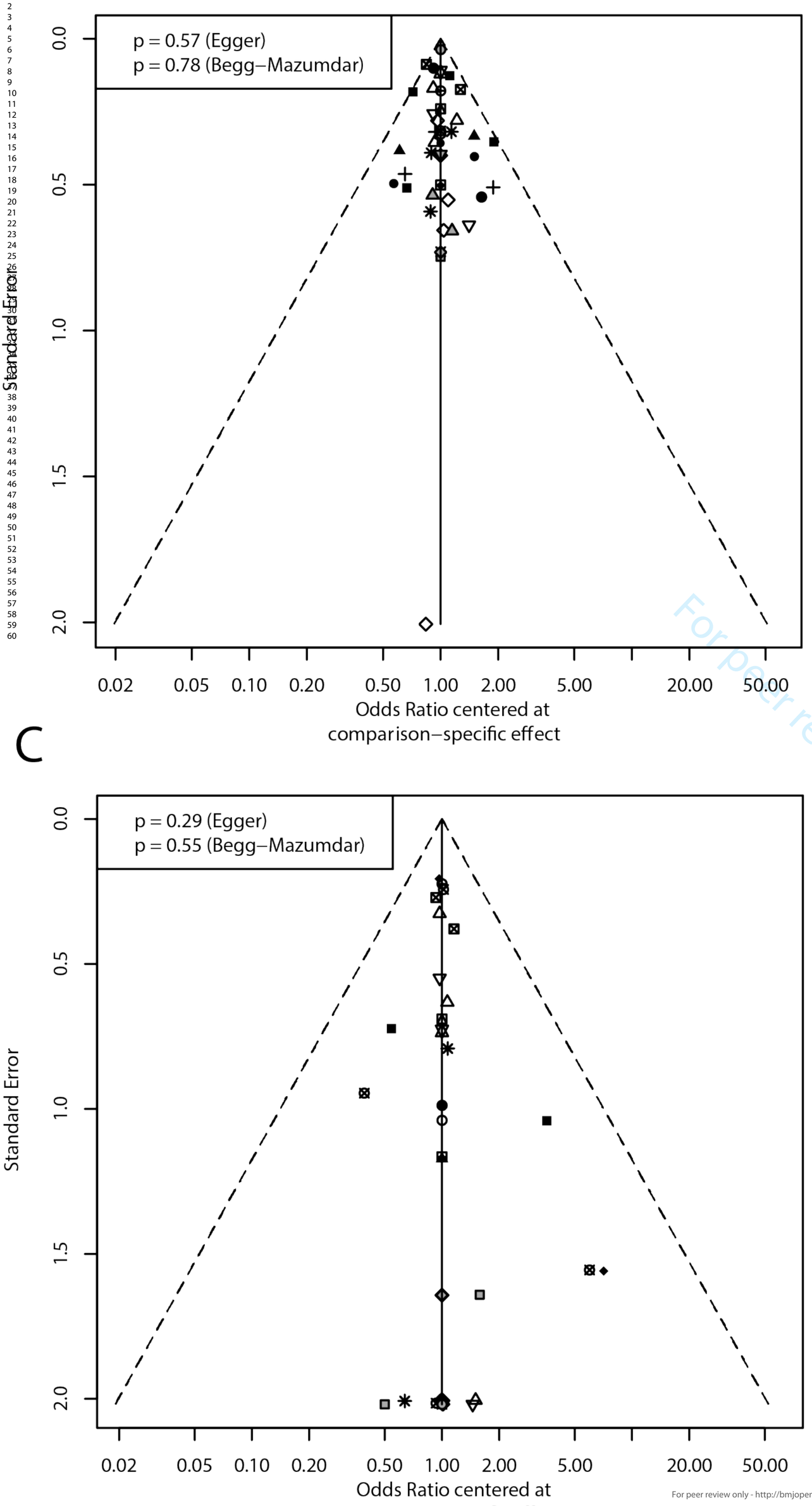

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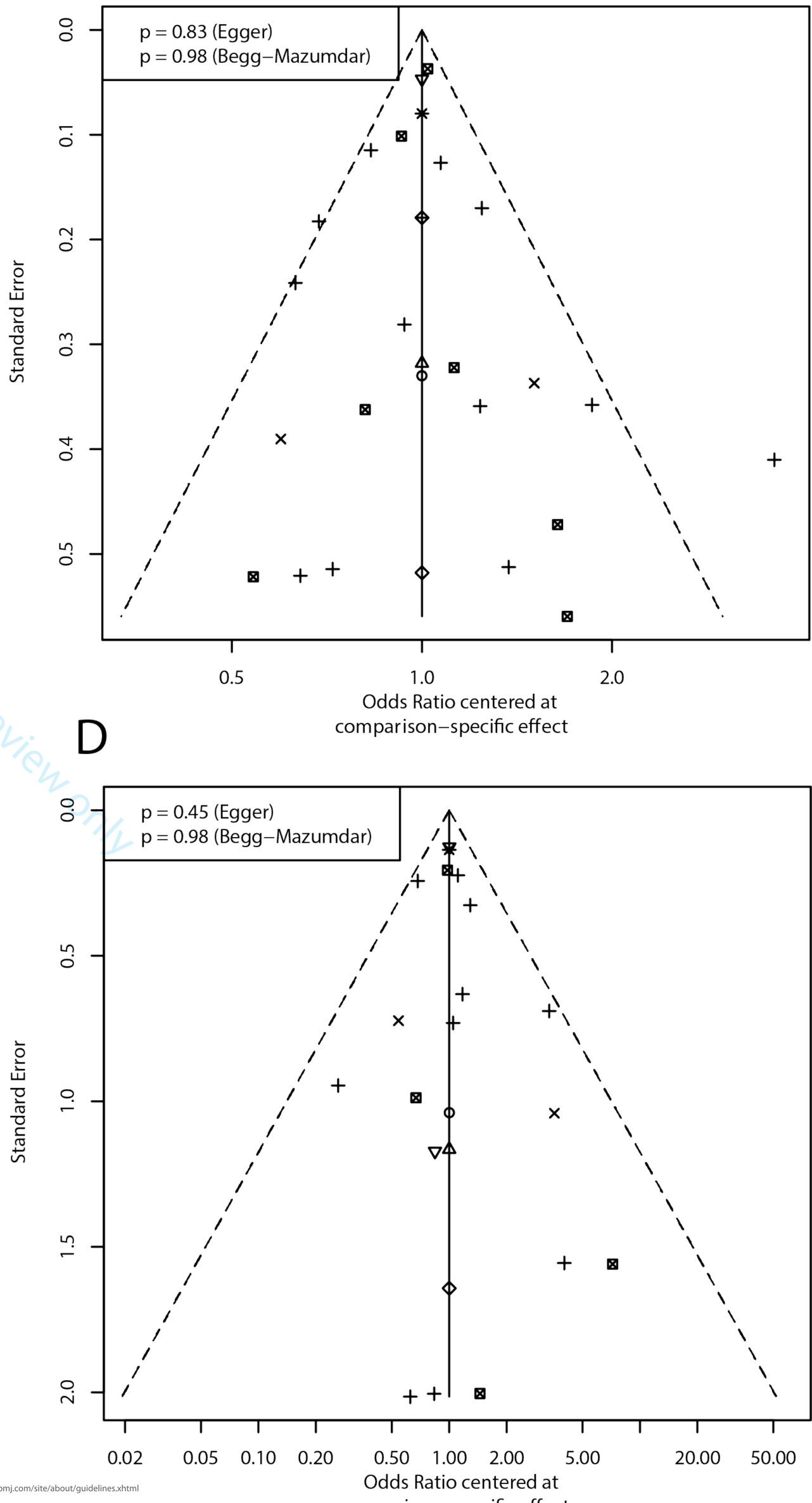

C

D

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1-4
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	11-41
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	16-17
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	20-23
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	24-31
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	19-22
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Figure1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	68-76
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	75-76
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	90-92
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	94-98
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	75-76
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	69-73
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	80-82
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	83-84
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	85-86
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	90-93
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	94-98
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	101-105
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	105-108
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	107-108

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	111-113
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	114-116
Study characteristics	17	Cite each included study and present its characteristics.	118-121
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	126-130
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	131-135
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	118-126
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	126-130
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	131-135
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	137-141
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	143-149
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	151-153
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	169-174
	23b	Discuss any limitations of the evidence included in the review.	176-179
	23c	Discuss any limitations of the review processes used.	181-184
	23d	Discuss implications of the results for practice, policy, and future research.	186-192
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	241-247
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	241-247
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	241-247
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	236
Competing interests	26	Declare any competing interests of review authors.	250
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	239

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

BMJ Open

Effectiveness of lipid-lowering therapy on mortality and major adverse cardiovascular event outcomes in patients undergoing percutaneous coronary intervention: a network meta-analysis of randomized controlled trials

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine, Pharmacology and therapeutics
Keywords:	Coronary heart disease < CARDIOLOGY, Coronary intervention < CARDIOLOGY, Lipid disorders < DIABETES & ENDOCRINOLOGY

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Effectiveness of lipid-lowering therapy on mortality and major adverse cardiovascular event outcomes in patients undergoing percutaneous coronary intervention: a network meta-analysis of randomized controlled trials

Chang-Jiang Deng[1], Ju Yan[2], Ying-Ying Zheng[1],Ting-Ting Wu[1], Ying Pan[1], Xian-Geng Hou[1],Si-Fan Wang[1], Subinur·Sirajidin[1], Mikereyi.Aimaitijiang[1],Xiang Xie[1]

1. Department of Cardiology, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, 830011, P.R. China.

2. Department of Cardiology, Shaanxi Provincial People's Hospital, Xi'an, 710000, P.R. China.

Correspondence authors:

Xiang Xie, No. 137, Liyushan Road, Department of Cardiology, First Affiliated Hospital of Xinjiang Medical University, Urumqi, 830011 P.R., China. Tel: +8609914366168; Email: xiangxie999@sina.com

Abstract

Background

Emergency percutaneous coronary intervention (PCI) can quickly restore myocardial perfusion after acute coronary syndrome (ACS). Whether and which lipid-lowering regimens are effective in reducing major adverse cardiovascular events (MACEs) and mortality risk after PCI remain unclear.

Objective

This study assessed the benefits of different lipid-lowering regimens on the risk of MACEs and mortality in the post-PCI population by network meta-analysis.

Methods

Public databases, including PubMed, Embase, and the Cochrane Library, were searched from inception to August 2022. Randomized controlled trials (RCTs) on lipid-lowering regimens in post-PCI populations were included and analysed. The outcomes were the incidence of all-cause mortality and MACEs, whether reported as dichotomous variables or as hazard ratios (HRs).

Results

Thirty-nine RCTs were included. For MACEs, alirocumab plus rosuvastatin (OR: 0.18; 95% CI: 0.07-0.44), evolocumab plus ezetimibe and statins (OR: 0.19; 95% CI: 0.06-0.59), eicosapentaenoic acid (EPA) plus pitavastatin (HR: 0.67; 95% CI: 0.49-0.96), and icosapent ethyl plus statins (HR: 0.73; 95% CI: 0.62-0.86) had significant advantages and relatively high rankings. For mortality, rosuvastatin (OR: 0.30; 95% CI: 0.11-0.84), ezetimibe plus statins (OR: 0.55; 95% CI: 0.43-0.89) and icosapent ethyl plus statins (OR: 0.66; 95% CI: 0.45-0.96) had significant advantages compared to the control.

Conclusion

EPA, especially icosapent ethyl, plus statins had a beneficial effect on reducing the risk of MACEs and mortality in post-PCI patients. PCSK9is plus statins were able to

reduce the risk of MACEs, but the risk of mortality remained unclear.

Key words: lipid-lowering therapy, major adverse cardiovascular events, mortality, network meta-analysis

Strengths and limitations of this study

The strengths of this study included the following:

only RCTs were considered for inclusion with high overall design quality;

MACE and mortality were adopted as outcomes;

the subjective factors of the investigator had little influence on the outcomes.

The limitations included the following:

this meta-analysis was based on the study level instead of the individual level;

the criteria for defining MACEs varied among studies;

many included studies only reported dichotomous outcomes but did not report the HR results.

Introduction

Acute coronary syndrome (ACS) is a term used to refer to a range of conditions associated with acute myocardial ischaemia and/or infarction, which are usually due to coronary artery occlusion and acute ischaemic necrosis of the myocardium due to progression of coronary atherosclerotic lesions(1, 2). Emergency percutaneous coronary intervention (PCI) can quickly restore myocardial perfusion(3). Although the development of technological and procedural PCI has resulted in substantial

improvements in clinical outcomes, recurrent coronary events may still occur after PCI(4).

The view of "residual cardiovascular risk" was introduced because MACEs still occurs in some patients who underwent PCI during follow-up. PCI can treat focal manifestations of systemic progressive disease, but the residual risk of acute coronary syndrome is largely related to the systemic proatherosclerotic effect of poorly controlled cardiovascular risk factors(4). Lowering lipid levels, especially LDL-C, can halt the progression of coronary atherosclerosis and improve cardiovascular outcomes. Based on this view, it is believed that long-term optimal lipid-lowering therapy is effective in reducing long-term cardiovascular events after PCI. However, this view was still subject to challenges.

Based on data from the “Korea Acute Myocardial Infarction Registry”, the proponents concluded that patients treated with statins had significantly lower rates of MACEs, all-cause death, and cardiac death during the 2-year follow-up period after PCI application(5). However, a study of postoperative follow-up of PCI patients enrolled in the Melbourne Interventional Group registry concluded that statins have no significant beneficial effect on MACEs after PCI(6). The controversy may be explained by two concepts: on the one hand, the optimal lipid reduction target may not be achieved by using single statins(7,8). On the other hand, long-term high-dose application of statins increases the risk of intracerebral haemorrhage and other side

effects(9,10).

There is a consensus on preloading high-dose statins to reduce MACEs in the perioperative period with PCI(11,12). However, there is still insufficient evidence for the continued application of lipid-lowering drugs to reduce the risk of long-term MACEs and mortality. This study assessed the benefits of different lipid-lowering regimens on the risk of MACEs and mortality in the post-PCI population by network meta-analysis.

Methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study was registered with PROSPERO (CRD 42018099600).

Patient and Public Involvement

None

Search strategy

Public literature databases, including PubMed, Embase, and the Cochrane Library, were searched from inception to August 2022 without language restrictions using the following search terms: (lipid-lowering or statin or simvastatin or rosuvastatin or atorvastatin or fluvastatin or lovastatin or pravastatin or pitavastatin or mevastatin or

ezetimibe or “eicosapentaenoic acid” or “icosapent ethyl” or “bempedoic acid” or fibrate or bezafibrate or gemfibrozil or fenofibrate or ciprofibrate or evolocumab or alirocumab or evinacumab or volanesorsen or vupanorsen or pelacarsen or olezarsen or inclisiran or olpasiran) and (“percutaneous coronary intervention” or “coronary angioplasty”) and (random* or randomized or randomized). The details of the full search strategy are listed in the Supplementary file. The references of relevant systematic reviews and meta-analyses were also searched to avoid omissions. The two authors conducted literature retrieval independently, and any conflicts were resolved through discussion with the third author.

Inclusion and exclusion criteria

The literature was included if it met the following criteria: 1) the study adopted a randomized controlled study design; 2) the study included patients who underwent PCI surgery or reported the subgroup of the population that underwent PCI; 3) the lipid-lowering regimen was applied to the population of the intervention group; 4) the control group used a different lipid-lowering agent or regimen; and 5) the study reported the outcome of mortality and/or MACEs. The exclusion criteria were as follows: 1) as preloading of statins before PCI was shown to have clear benefits, to determine whether application of lipid-lowering drugs after PCI also had beneficial effects, this work excluded studies on the preloading application of lipid-lowering drugs before PCI; and 2) although high-dose lipid-lowering agents, such as statins,

have a better lipid-lowering effect, long-term application may bring potential side effects(9,13). Therefore, only studies in which all agents were considered to be applied at reasonable doses were included, and dose–response studies were excluded. In addition, repeatedly published studies, protocols, conference abstracts, reviews, comments and editorials were also excluded.

Data extraction and quality assessment

Two authors independently extracted the information from the included studies. The contents include the name of the first author, publication year, study location, sample size (population that underwent PCI), study abbreviation and registration number, lipid-lowering intervention and control, and follow-up time.

The outcomes analysed were the incidence of all-cause mortality and MACEs, whether reported as dichotomous or hazard ratio (HR) statistics based on Cox regression. The MACE outcome was selected to most closely approximate the composite endpoint, including mortality, MI, stroke, coronary revascularization, and restenosis. Study quality was assessed by two investigators using the Cochrane risk of bias assessment tool, which included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential biases.

Statistical analysis

We conducted frequentist network meta-analysis (NMA) using random-effects models weighted by the inverse variance method. Odds ratios (ORs) and 95% confidence intervals (CIs) were used for dichotomous outcomes. The hazard ratios (HRs) and 95% CIs based on Cox regression results were also pooled for reporting. If the HR value was not reported but there was a Kaplan–Meier survival curve, the HR value was extracted from the curve by GetData Graph Digitizer software version 2.24. In network plots, the direct comparisons among treatment arms are shown, the end of each line indicates a treatment arm, and the thickness of the lines indicates the number of studies comparing the two treatments. Forest plots were used to describe the network comparison results between each treatment and the control.

The restricted maximum likelihood estimation was used to quantify network heterogeneity. The Q statistic was used to assess the sum of statistics for heterogeneity (within designs) and for overall inconsistency (between designs)(14). The ranking probabilities of each regimen were estimated using the surface under the cumulative ranking curve (SUCRA), which was the ratio of the area under the curve to the entire area. A comparison-adjusted funnel plot was used to examine potential publication biases in the NMA. P values of less than 0.05 were considered to indicate statistical significance. The NMA was performed using R language with the "netmeta" package.

Results

After removing duplicates, we obtained 1588 literature items. After screening the titles and abstracts, 1515 irrelevant studies were excluded. Seventy-three articles were screened for full text. The following articles were excluded: dose–response studies (8); those where no PCI population or subgroup was reported (6); those where no mortality or MACE-related outcomes were reported (6); repeated publications (5); studies related to preloading of lipid-lowering agents (4); studies unrelated to lipid-lowering agents (3); a protocol study (1); and a study with a non-RCT design (1). Finally, 39 articles were included, containing 54478 post-PCI patients (15-53) (Figure 1).

Table 1. The characteristics of included studies

Study	Location	Sample size	Abbreviation	Register ID	Intervention	Control	Follow-up#
Lorenz Räber 2022 [15]	European	300	PACMAN-AMI	NCT03067844	Alirocumab;rosuvastatin	Placebo;rosuvastatin	52W
Peterson, B. E. 2022 [16]	Multicenter	3408	REDUCE-IT PCI	NCT01492361	Icosapent ethyl;statins	Placebo;statins	4.8Y
Remo H.M. Furtado 2022 [17]	Multicenter	17073	FOURIER	NCT01764633	Evolocumab;statins	Placebo;statins	2.2Y
Tomoaki Okada 2022 [18]	Japan	102	-	UMIN000028729	Evolocumab;pitavastatin	Pitavastatin	4W
Yan Hao 2022 [19]	China	136	-	-	Evolocumab;atorvastatin;ezetimibe	Ezetimibe;atorvastatin	3M
Deng YF 2021 [20]	China	90	-	-	Ezetimibe;atorvastatin	Atorvastatin	1Y
Sun C 2021 [21]	China	171	-	ChiCTR-IPR-17012219	Ezetimibe;rosuvastatin	Rosuvastatin	3M
Weifeng He 2020 [22]	China	192	-	-	Atorvastatin vs. Rosuvastatin vs. Simvastatin	-	6M
Kiyoshi Hibi 2018 [23]	Japan	128	Ezetimibe-ACS	NCT00549926	Ezetimibe;pitavastatin	Pitavastatin	1Y
Eui Im 2017 [24]	Korea	2000		NCT01557075	Atorvastatin	Pravastatin	1Y
Hagiwara N 2017 [25]	Japan	1734	HIJ-PROPER	UMIN000002742	Ezetimibe;pitavastatin	Pitavastatin	36M
J Guo 2017 [26]	China	137	-	-	Rosuvastatin	Control	1Y

Wang YB 2017 [27]	China	132	-	ChiCTR-IPR-15007035	Pitavastatin	Atorvastatin	6M
Watanabe T 2017 [28]	Japan	193	CHERRY	UMIN000002815	EPA;pitavastatin	Pitavastatin	6-8M
Zhi Liu 2017 [29]	China	102	-	-	Ezetimibe;atorvastatin	atorvastatin 20mg/d	1Y
Kazumasa Nosaka 2016 [30]	Japan	241	-	UMIN000016723	EPA;pitavastatin	Pitavastatin	1Y
Kensuke Matsushita 2016 [31]	Japan	118	Yokohama-ACS	NCT00549926	Atorvastatin vs. Pitavastatin vs. Pravastatin vs. Fluvastatin	-	10.3M
Christopher P Cannon 2015 [32]	Multicenter	12941	IMPROVE-IT	NCT00202878	Ezetimibe;simvastatin	Simvastatin	6M
Kenichi Tsujita 2015 [33]	Multicenter	246	PRECISE-IVUS	NCT01043380	Ezetimibe;atorvastatin	Atorvastatin	1Y
Stephen J. Nicholls 2015 [34]	Multicenter	3295	VISTA-16	NCT01130246	Varespladib;atorvastatin	Placebo;atorvastatin	6M
Zhang JR 2015 [35]	China	104	-	-	Atorvastatin	Rosuvastatin	6M
Mario Leoncin 2014 [36]	Italy	333	PRATO-ACS	NCT01185938	Rosuvastatin	Control	6M
Hiroyuki Takano 2013 [37]	Japan	458	PEARL	UMINC000000428	Pitavastatin	Control	35.5M
Tsuyoshi Nozue 2013 [38]	Japan	164	TRUTH	UMIN000004627	Pitavastatin	Pravastatin	2Y
Jean-Marc Lablanche 2010 [39]	Multicenter	887	CENTAURUS	NCT00296387	Rosuvastatin	Atorvastatin	3M
C. Michael Gibson 2009 [40]	US	2868	PROVE IT-TIMI 22	NCT00382460	Atorvastatin	Provastatin	2Y
Han Yaling 2009 [41]	China	1275	-	NCT00405717	Atorvastatin	Provastatin	1Y
Takafumi Hiro 2009 [42]	Japan	307	JAPAN-ACS	NCT00242944	Pitavastatin	Atorvastatin	1Y
Tomotaka Dohi 2009 [43]	Japan	180	Extended-ESTABLISH trial	-	Atorvastatin	Control	4Y
Toru Toi 2009 [44]	Japan	160	-	-	Pitavastatin	Atorvastatin	17D
Xu Kai 2007 [45]	China	648	-	-	Atorvastatin	Control	2Y
Bae JH 2004 [46]	Korea	205	-	-	Atorvastatin	Control	6M
Patrick W J C Serruys 2002 [47]	Multicenter	1677	LIPS	-	Fluvastatin	Placebo	3.9Y
Han J.G.H. Mulder 2000 [48]	Netherland	201	REGRESS	-	Pravastatin	Placebo	2Y
Greg C. Flaker 1999 [49]	Multicenter	1154	CARE trial	-	Pravastatin	Placebo	6Y
MICHEL E. BERTRAND 1997 [50]	France	695	PREDICT	-	Pravastatin	Placebo	6M
J H O'Keefe Jr 1996 [51]	US	200	APPLE	-	Probucol;lovastatin	Placebo	6M
Haruhiko Onaka 1994 [52]	Japan	66	-	-	Pravastatin	Control	5M
Rakesh Sahni 1991 [53]	US	157	-	-	Lovastatin	Control	6M

Abbreviations: EPA: eicosapentaenoic acid.

#: Follow-up period: Y: years; M: months; W: weeks; D: days

Among the included studies, the publication period ranged from 1991 to 2022. The research locations were mainly in Asia (China, Japan and South Korea), Europe (Netherlands, France, and Italy), America, and multiple centres. There were 10 studies with sample sizes greater than 1000 patients. There were also 22 studies with publicly available clinical study registration numbers (Table 1). In terms of design quality, all included studies were RCTs. Therefore, the design quality was generally high. The main factors potentially affecting design quality were the blinding of participants and personnel and blinding of outcome assessment (Figure 2). However, as the desired outcomes were mortality and MACEs, the subjective factors of the investigator had little influence on the outcomes.

As two studies did not specify the types of statins, the network meta-analysis was divided into two parts. One part was analysed based on specific types of statins, and the other was based on taking statins as a whole. For the dichotomous results of MACEs, the NMA based on specific types of statins included 18 lipid-lowering regimens. The Q test for heterogeneity ($p = 0.07$) and inconsistency ($p = 0.16$) were nonsignificant, indicating no evidence of heterogeneity or inconsistency in the NMA.

In pairwise comparisons with the control, alirocumab plus rosuvastatin (OR: 0.18; 95% CI: 0.07-0.44; SUCRA: 0.94), evolutionab plus atorvastatin and ezetimibe (OR: 0.18; 95% CI: 0.05-0.63; SUCRA: 0.90), and ezetimibe plus rosuvastatin (OR: 0.29; 95% CI: 0.11-0.76; SUCRA: 0.80) had significant advantages and relatively high

SUCRA rankings. No potential publication bias was found according to the comparison-adjusted funnel plot (Figure 3).

In the NMA based on taking statins as a whole, ten regimens were analysed. Evolocumab plus ezetimibe and statins (OR: 0.19; 95% CI: 0.06-0.59; SUCRA: 0.92), alirocumab plus statins (OR: 0.27; 95% CI: 0.13-0.59; SUCRA: 0.87), and icosapent ethyl plus statins (OR: 0.39; 95% CI: 0.25-0.62; SUCRA: 0.72) had significant advantages and relatively high SUCRA rankings. No potential publication bias was found.

For the HR results of MACEs, the NMA based on specific types of statins included nine regimens. The Q test for heterogeneity was nonsignificant ($p = 0.964$) because the network comparisons lacked loops. Therefore, the results were considered consistent. Compared to the control, eicosapentaenoic acid (EPA) plus pitavastatin (HR: 0.67; 95% CI: 0.49-0.96; SUCRA: 0.91), atorvastatin (HR: 0.76; 95% CI: 0.63-0.90; SUCRA: 0.83), and varespladib plus atorvastatin (HR: 0.77; 95% CI: 0.61-0.97; SUCRA: 0.77) had significant advantages and relatively high SUCRA rankings. Potential publication bias was not analysed due to the small number of included studies.

In the NMA based on taking statins as a whole, seven regimens were analysed. EPA

plus statins (HR: 0.60; 95% CI: 0.42-0.85; SUCRA: 0.96) and icosapent ethyl plus statins (HR: 0.73; 95% CI: 0.62-0.86; SUCRA: 0.81) had significant advantages over the control.

For the dichotomous mortality results, the NMA based on specific types of statins included 17 lipid-lowering regimens. The Q test for heterogeneity ($p = 0.78$) and inconsistency ($p = 0.99$) were nonsignificant. Due to the rare occurrence of events, the results of the comparison had low precision with a large standard error. Compared to the control, only rosuvastatin (OR: 0.30; 95% CI: 0.11-0.84; SUCRA: 0.79) showed a significantly better effect. Ezetimibe plus rosuvastatin had a relatively high SUCRA ranking, but there was no significant difference compared to the control (OR: 0.14; 95% CI: 0.02-1.26; SUCRA: 0.86). No potential publication bias was found (Figure 4).

In the NMA based on taking statins as a whole, nine regimens were analysed. Ezetimibe plus statins (OR: 0.55; 95% CI: 0.43-0.89; SUCRA: 0.75) and icosapent ethyl plus statins (OR: 0.66; 95% CI: 0.45-0.96; SUCRA: 0.63) had significant advantages compared with the blank control group. No potential publication bias existed. NMA analysis was not performed due to the small number of studies reporting HRs for mortality (Figure 5).

Discussion

This study analysed the benefits of lipid-lowering therapy on mortality and MACE outcomes in patients who underwent PCI by network meta-analysis. The results showed that several lipid-lowering regimens could reduce the risk of MACEs compared with the blank control. Icosapent ethyl plus statins had the benefit of reducing both the risk of MACEs and mortality. However, EPA plus statins had more advantages in reducing the risk of MACEs. Of note, based on the current evidence, alirocumab and evolocumab plus statins had obvious advantages in reducing the risk of MACEs but had no obvious benefit in reducing the risk of mortality.

EPA is a long-chain omega-3 polyunsaturated fatty acid. Long-term intake of EPA can reduce the residual cardiovascular risk to reduce the risk of MACEs(54). In terms of pathological mechanisms, EPA combined with pitavastatin was shown to reduce the lipid volume of coronary artery plaques and total atherosclerotic plaque volume in patients who underwent PCI, which may be the reason for the reduced risk of MACEs(55).

Icosapent ethyl is a highly purified and stable eicosapentaenoic acid ethyl ester that has potential higher anti-inflammatory, antioxidant, plaque stability and cell membrane stability effects(56). In the NMA results, icosapent ethyl plus statins had significant benefits for reducing the risk of either mortality or MACEs in patients who

underwent PCI, which was an ideal regimen for the population.

Ezetimibe inhibits the absorption of cholesterol and has a synergistic lipid-lowering pharmacological effect with statins to further reduce the risk of death and MACEs. In particular, when combined with rosuvastatin, ezetimibe has a stronger lipid-lowering effect with a high safety profile without the risk of drug interactions(57). Our NMA results also showed that ezetimibe can reduce the risk of MACEs and mortality. According to the guidelines for the management of dyslipidaemia from the European Society of Cardiology and the European Atherosclerosis Society, ezetimibe was recommended if the LDL-C target was not reached(58,59). The American College of Cardiology guidelines also recommend adding ezetimibe when using maximally tolerated statin therapy and if LDL-C levels remained ≥ 70 mg/dL(60). These benefits have also been demonstrated in the secondary prevention of PCI.

Alirocumab and evolocumab are both proprotein convertase subtilisin/kexin type-9 inhibitors (PCSK9is), which can increase the level of LDL receptor in the liver, thus improving the ability of the liver to bind LDL-C and reducing the level of peripheral LDL-C(61). There was also a synergistic lipid-lowering pharmacological effect when PCSK9is were combined with statins that resulted in a significantly reduced LDL-C concentration and atherosclerosis event risk; however, there was still controversy regarding the mortality risk reduction(62). It has been suggested that the powerful

effect of PCSK9is on reducing LDL-C predisposes patients to hypocholesterolaemia, which will not increase the risk of cerebral haemorrhage. PCSK9is may be the preferred lipid-lowering agents in patients with elevated ICH risk (63-65). On the other hand, PCSK9is did not reduce serum inflammatory factors in one study, suggesting that they may not reduce the risk of residual inflammation in the post-PCI population(66).

In the results of this study, lipid-lowering therapy strategies had general advantages in reducing MACE risk. However, for all-cause mortality, the advantage of lipid-lowering therapy was not obvious. Based on dichotomous outcomes of mortality, some strategies may even have a tendency to increase the mortality risk. This challenges the opinion that lipid-lowering therapy is recommended after PCI(67). A large sample size retrospective study suggests that statins can reduce the risk of all-cause death in patients with coronary artery disease undergoing PCI, regardless of individual cholesterol levels(68). Alternatively, the “lipid paradox” view has been proposed and indicates that higher levels of LDL-C and triglycerides on admission are associated with better clinical outcomes. Especially in patients with ST-elevation myocardial infarction, lower LDL-C levels were associated with worse mortality outcomes(69). However, this view is also controversial(70).

On the other hand, it is possible that the contribution of LDL-C reduction to the risk

of mortality outcomes is obscured by other confounding factors. For example, inflammatory status may also have had an important impact on patient mortality risk. In a cohort of post-PCI patients with low LDL-C levels, residual inflammatory risk also had a significant effect on overall mortality(71). C-reactive protein can also predict long-term mortality in post-PCI patients independent of LDL-C levels(72). In addition, cardiac remodelling also has an important impact on the survival outcome of post-PCI patients(73).

There are several limitations in this study. First, this analysis was based on the study level instead of the individual level, making it difficult to consider the individual confounding factors in the analysis. Second, two included studies did not specify the type of statins, so our study had to be analysed separately according to whether all statins were considered as a whole. Third, the criteria for defining MACEs varied among studies, which contributed to heterogeneity among the study results. Fourth, many included studies only reported dichotomous outcomes but did not report the HR results, resulting in missing relevant data for the analysis.

In conclusion, the results of this study suggested that EPA, especially icosapent ethyl, plus statins had a beneficial effect on reducing the risk of MACEs and mortality in post-PCI patients. PCSK9is plus statins were able to reduce the risk of MACEs, but the effects on the risk of mortality remained unclear.

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Author contributions

Chang-Jiang Deng completed the manuscript, Ju Yan, Ting-Ting Wu,Ying Pan,Ying-Ying Zheng guided the data analysis and the production of the figures, Xian-Geng Hou,Si-Fan Wang, Subinur·Sirajidin, Mikereyi.Aimaitijiang,Xiang Xie read and approved the fnal manuscript.

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Availability of data and materials

the datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study does not involve human participants and ethical approval was not required.

Consent for publication

not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figure 1. Flowchart of the study selection process for eligible studies

Figure 2. Methodological quality assessment of included studies

Figure 3. Network plots of comparisons for major outcomes included in the analyses. A: dichotomous results of MACE based on specific types of statins; B: dichotomous results of MACE based on taking statins as a whole; C: hazard ratio results of MACE

based on specific types of statins; D: hazard ratio results of MACE based on taking statins as a whole; E: dichotomous results of mortality based on specific types of statins; F: dichotomous results of mortality based on taking statins as a whole.

Figure 4. Forest plots of lipid-lowering therapy compare to control for outcomes in network meta-analysis with SUCRA ranking results. A: dichotomous results of MACE based on specific types of statins; B: dichotomous results of MACE based on taking statins as a whole; C: hazard ratio results of MACE based on specific types of statins; D: hazard ratio results of MACE based on taking statins as a whole; E: dichotomous results of mortality based on specific types of statins; F: dichotomous results of mortality based on taking statins as a whole.

Figure 5. The comparison-adjusted funnel plot for assessing all main outcomes. A: dichotomous results of MACE based on specific types of statins; B: dichotomous results of MACE based on taking statins as a whole; C: dichotomous results of mortality based on specific types of statins; D: dichotomous results of mortality based on taking statins as a whole.

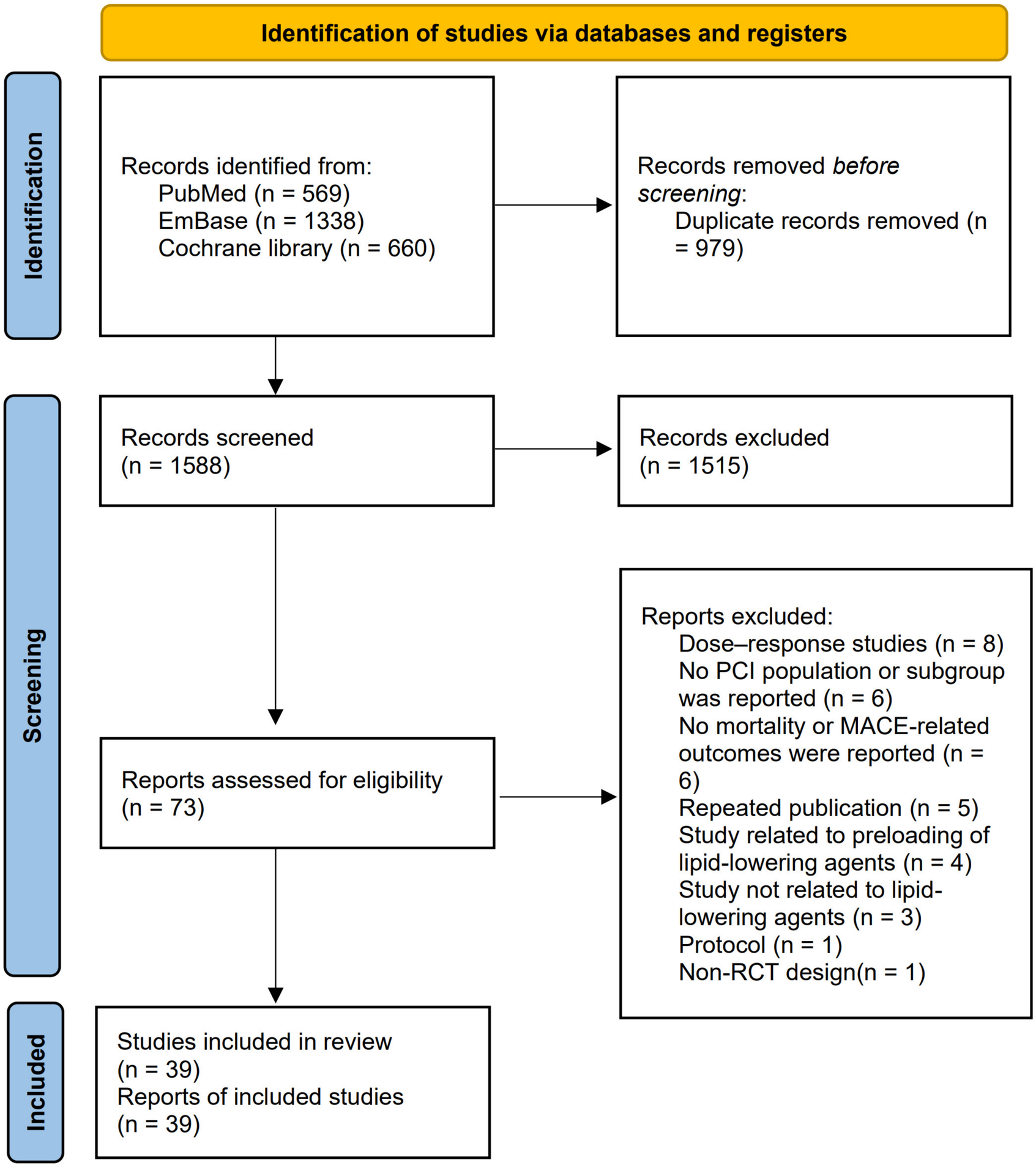
Authors and Afliations

Chang-Jiang Deng, Ju Yan, Ying-Ying Zheng,Ting-Ting Wu, Ying Pan, Xian-Geng Hou,Si-Fan Wang, Subinur·Sirajidin, Mikereyi·Sirajidin,Xiang Xie

Chang-Jiang Deng	Xian-Geng Hou
1187229853@qq.com	380138554@qq.com
Ju Yan	Si-Fan Wang
yyjj2017@163.com	562654119@qq.com
Ying-Ying Zheng	Subinur·Sirajidin
zhengying527@163.com	496568064@qq.com
Ting-TingWu	Mikereyi·Aimaitijiang
1255723526@qq.com	3195676352@qq.com
Ying Pan	Xiang Xie
2475854195@qq.com	xiangxie999@sina.com

Department of Cardiology, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, 830011, P.R. China.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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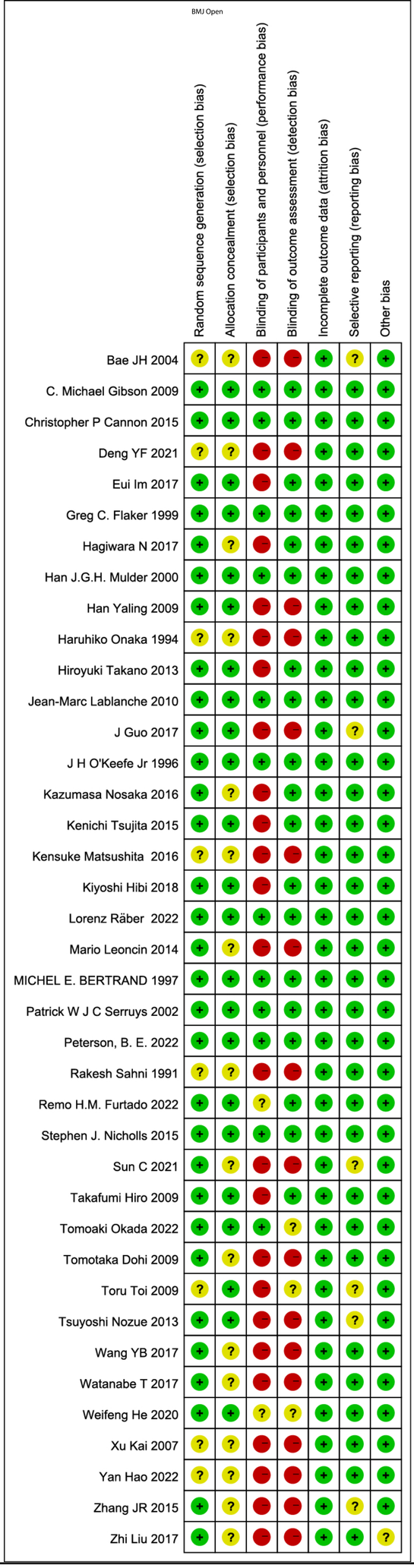
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Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Bae JH 2004
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Christopher P Cannon 2015
Deng YF 2021
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Greg C. Flaker 1999
Hagiwara N 2017
Han J.G.H. Mulder 2000
Han Yaling 2009
Haruhiko Onaka 1994
Hiroyuki Takano 2013
Jean-Marc Lablanche 2010
J Guo 2017
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Kenichi Tsujita 2015
Kensuke Matsushita 2016
Kiyoshi Hibi 2018
Lorenz Räber 2022
Mario Leoncin 2014
MICHEL E. BERTRAND 1997
Patrick W J C Serruys 2002
Peterson, B. E. 2022
Rakesh Sahni 1991
Remo H.M. Furtado 2022
Stephen J. Nicholls 2015
Sun C 2021
Takafumi Hiro 2009
Tomoaki Okada 2022
Tomotaka Dohi 2009
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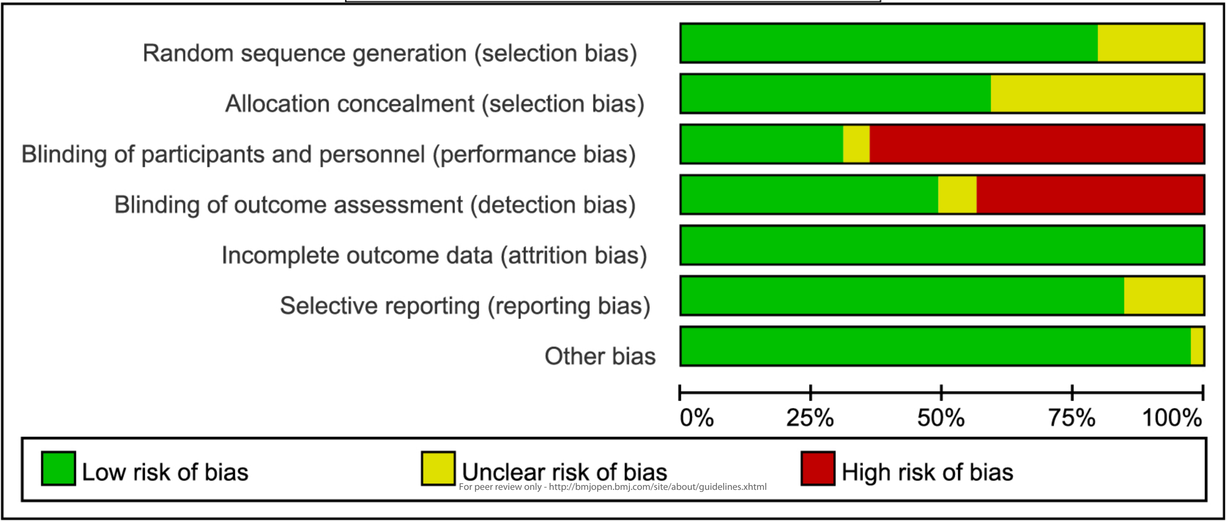
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Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
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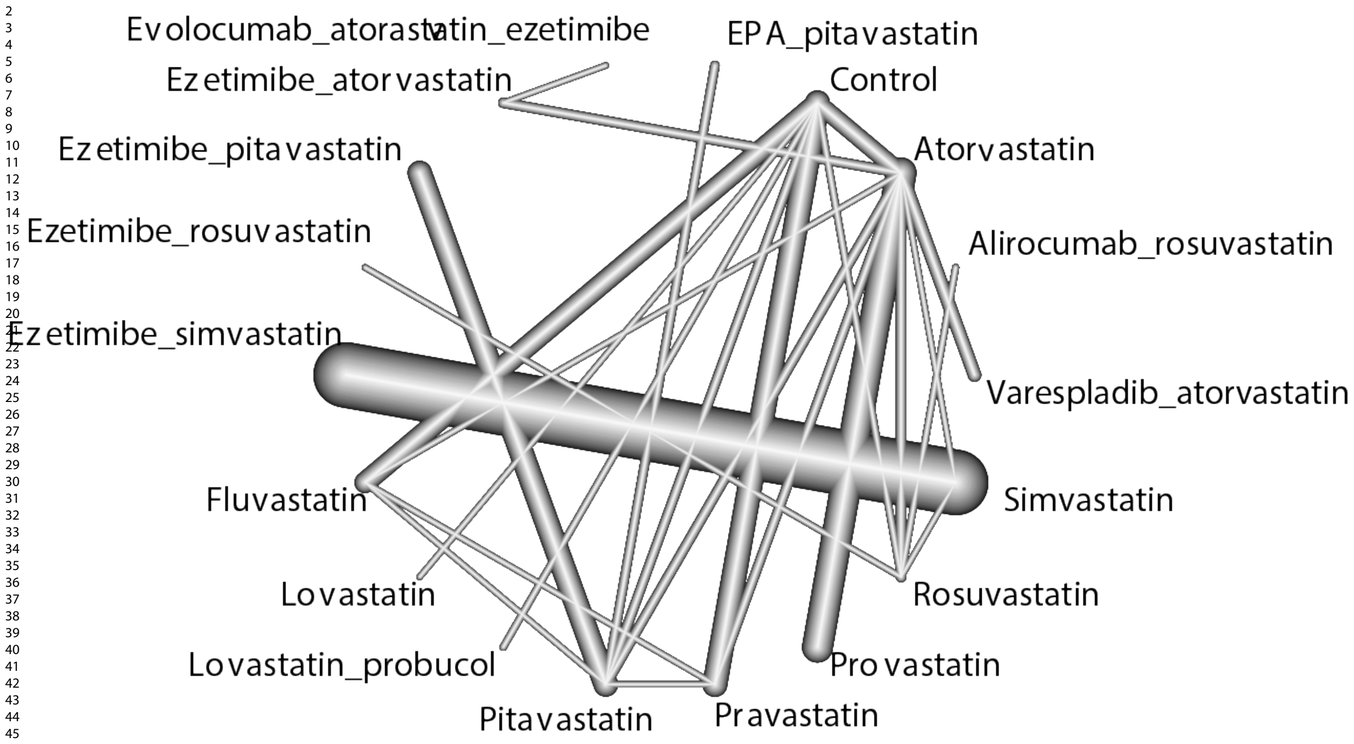
100%
Low risk of bias
Unclear risk of bias
High risk of bias

A



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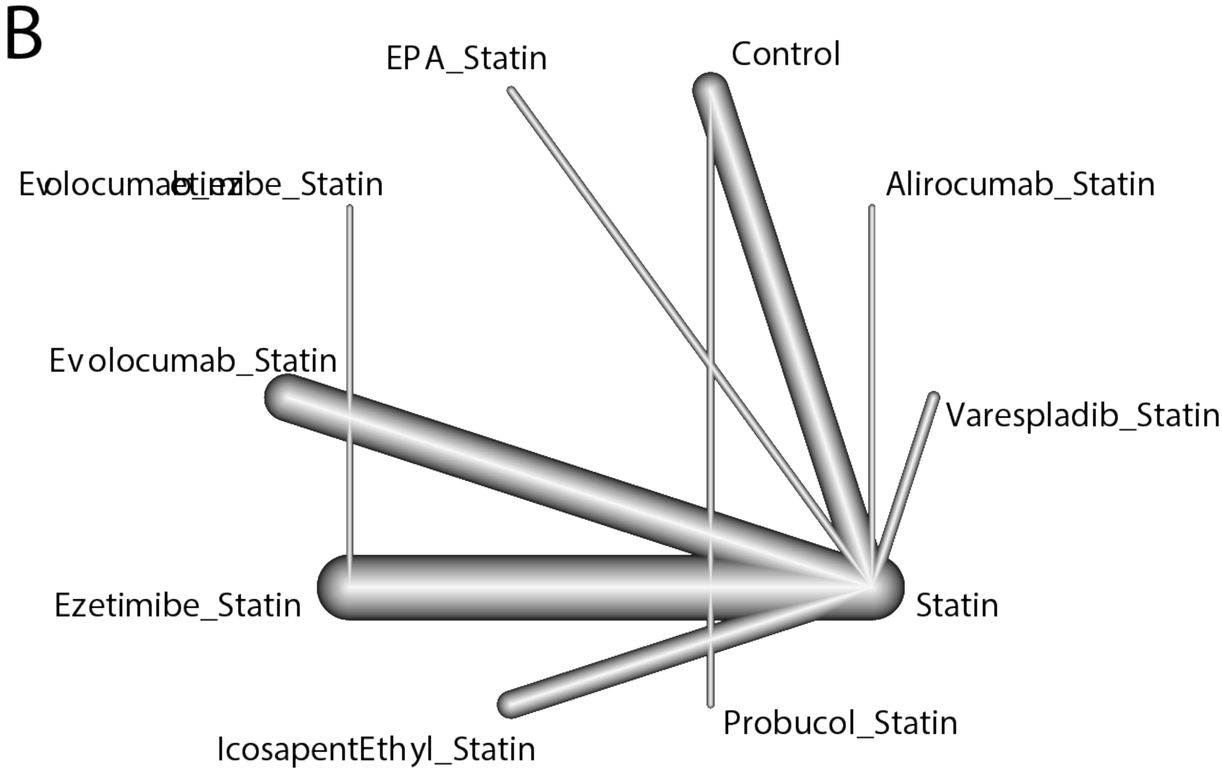

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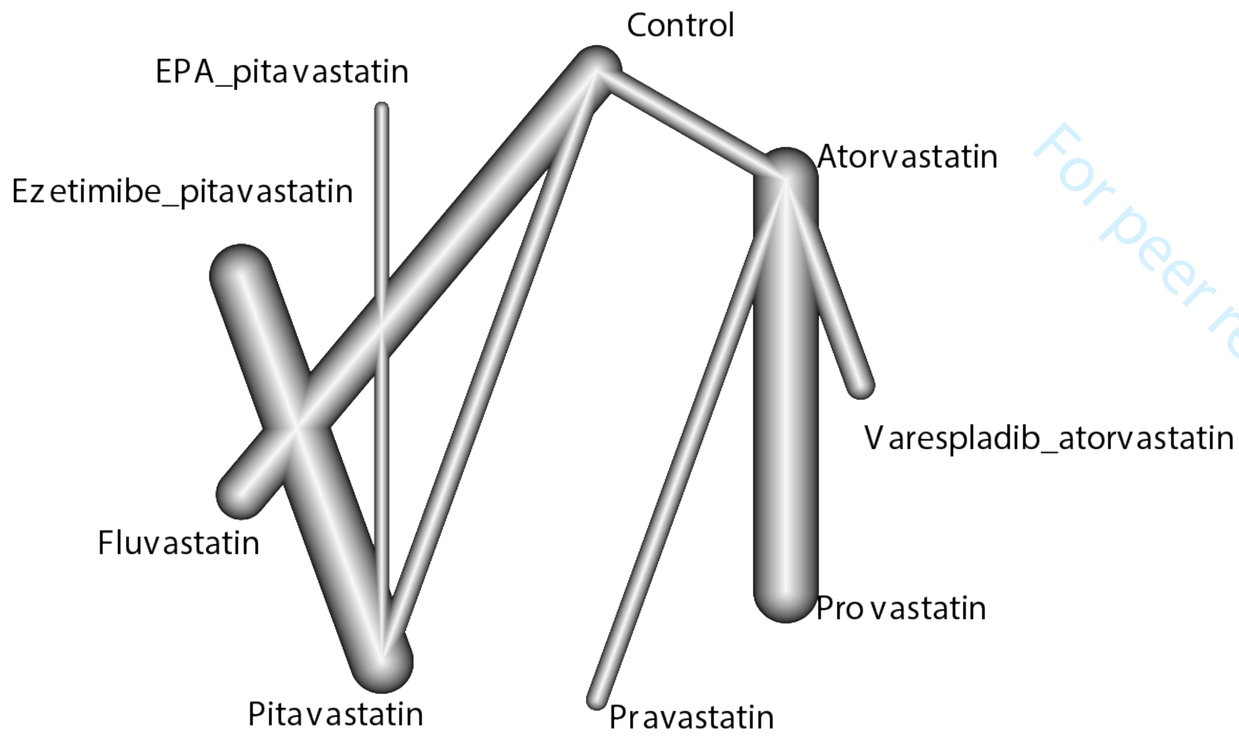

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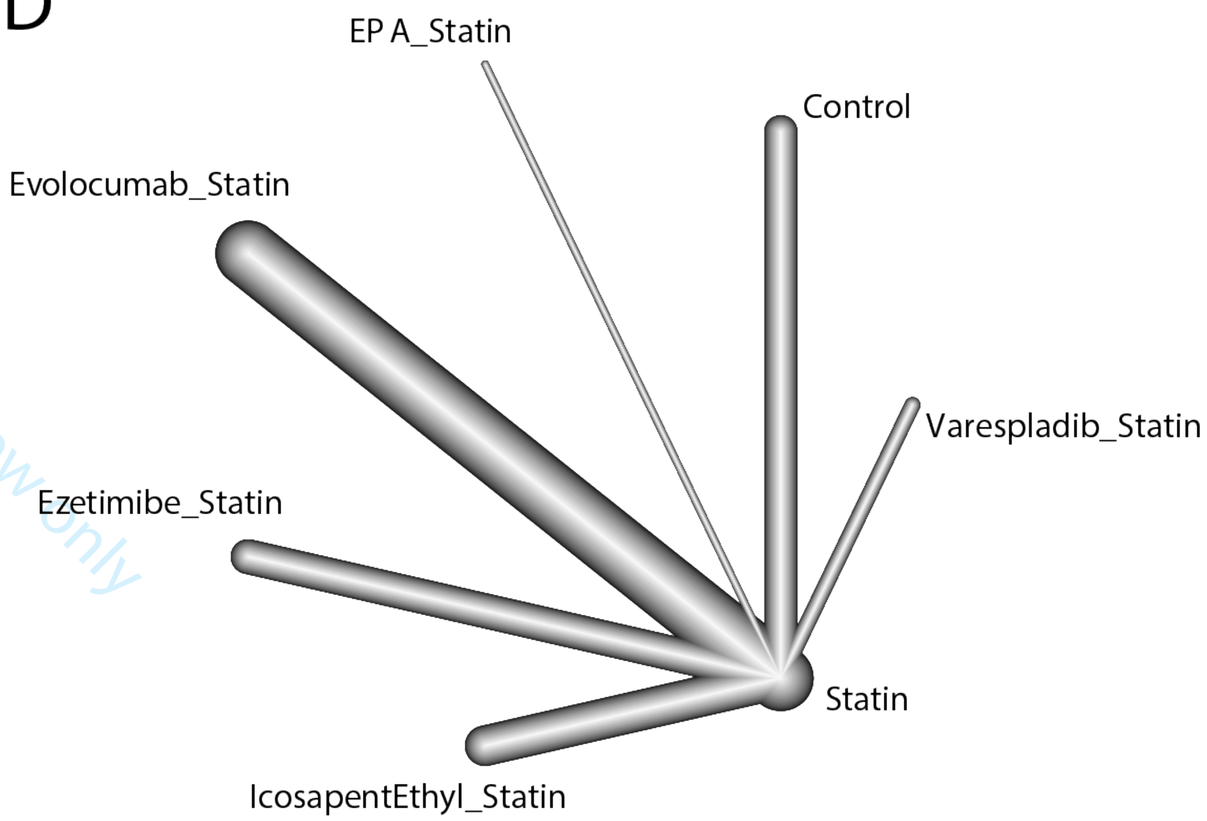

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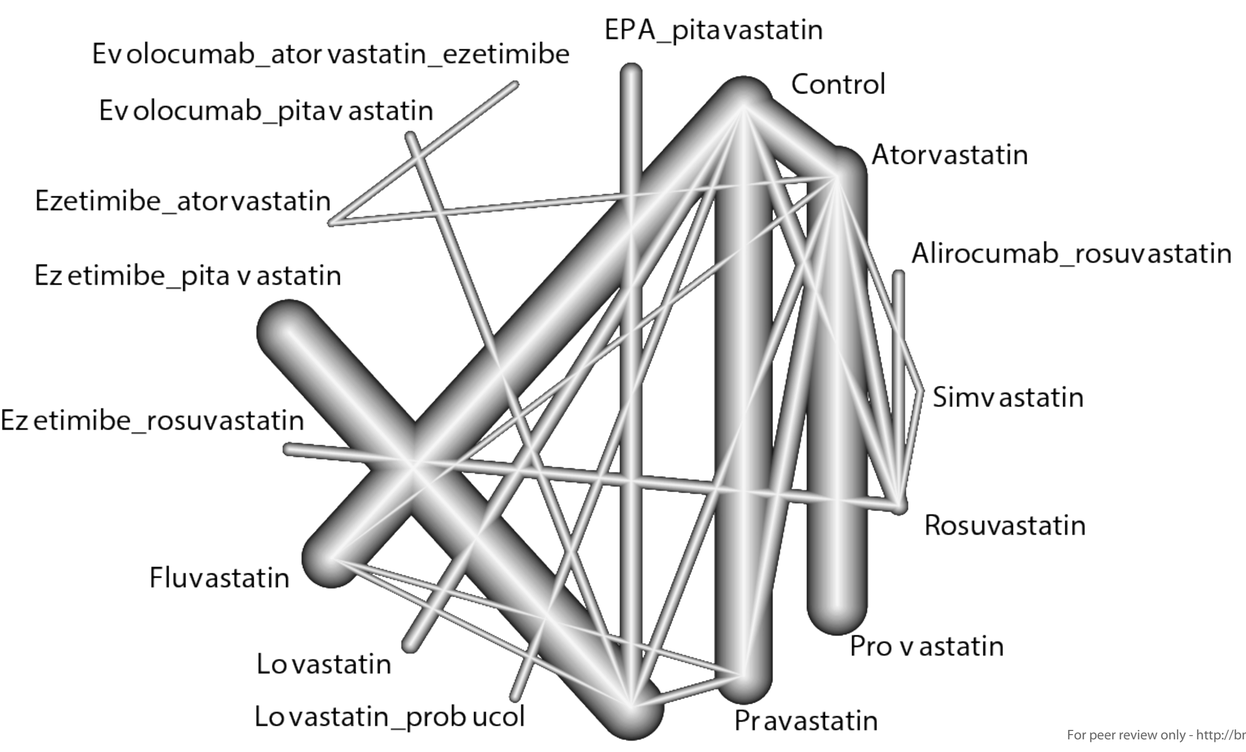

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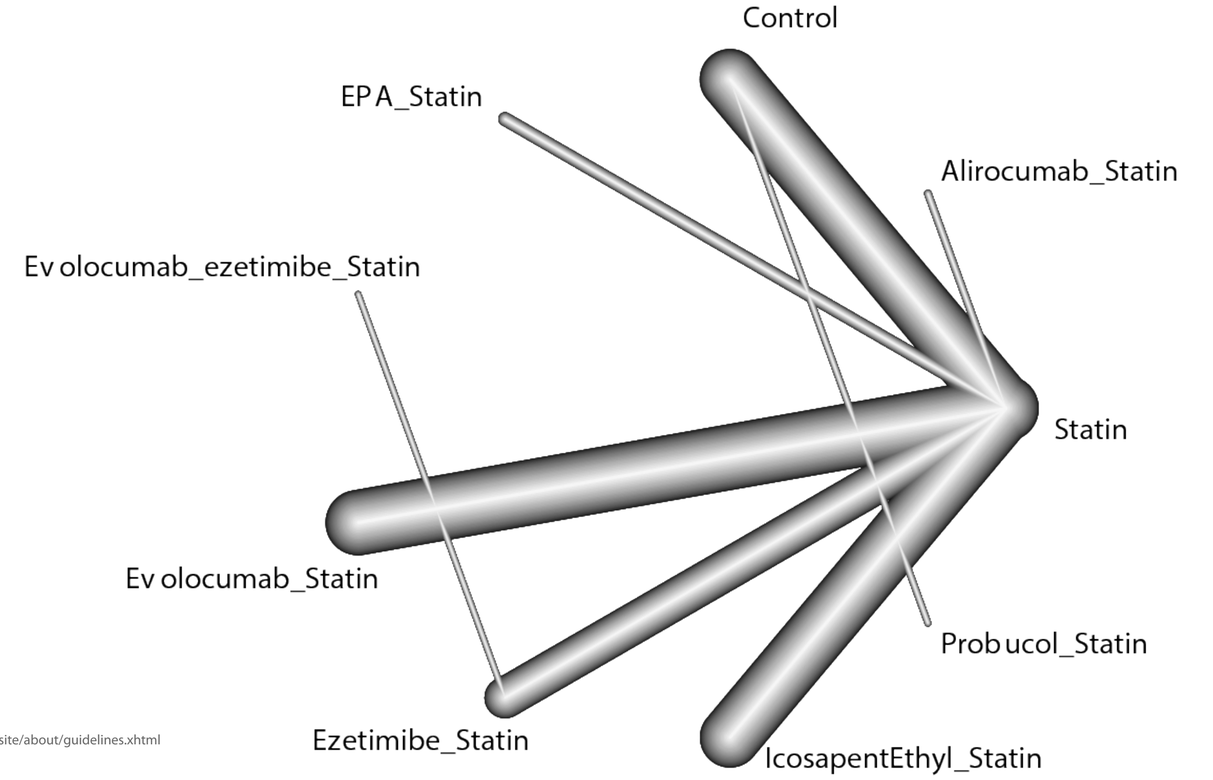
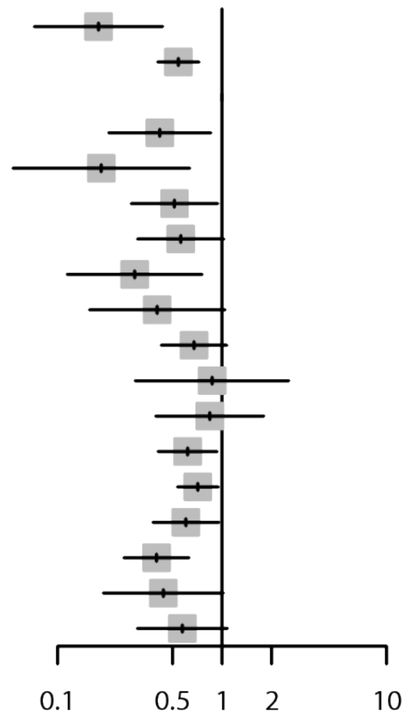


A

Comparison: other vs 'Control' (Random Effects Model)

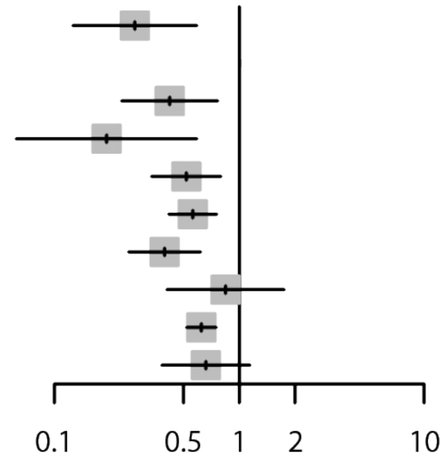
Treatment	OR	95%–CI	SUCRA
Alirocumab_rosuvastatin	0.18	[0.07; 0.44]	0.94
Atorvastatin	0.54	[0.41; 0.72]	0.49
Control	1.00		0.06
EPA_pitavastatin	0.42	[0.20; 0.85]	0.65
Evolocumab_atorvastatin_ezetimibe	0.18	[0.05; 0.63]	0.90
Ezetimibe_atorvastatin	0.51	[0.28; 0.94]	0.54
Ezetimibe_pitavastatin	0.56	[0.31; 1.03]	0.45
Ezetimibe_rosuvastatin	0.29	[0.11; 0.76]	0.80
Ezetimibe_simvastatin	0.40	[0.16; 1.04]	0.65
Fluvastatin	0.67	[0.43; 1.07]	0.31
Lovastatin	0.87	[0.30; 2.55]	0.22
Lovastatin_probucol	0.84	[0.39; 1.79]	0.20
Pitavastatin	0.62	[0.41; 0.93]	0.37
Pravastatin	0.71	[0.54; 0.95]	0.25
Provastatin	0.60	[0.38; 0.95]	0.39
Rosuvastatin	0.40	[0.25; 0.63]	0.71
Simvastatin	0.44	[0.19; 1.02]	0.63
Varespladib_atorvastatin	0.57	[0.31; 1.08]	0.43



B

Comparison: other vs 'Control' (Random Effects Model)

Treatment	OR	95%–CI	SUCRA
Alirocumab_Statin	0.27	[0.13; 0.59]	0.87
Control	1.00		0.05
EPA_Statin	0.42	[0.23; 0.76]	0.66
Evolocumab_ezetimibe_Statin	0.19	[0.06; 0.59]	0.92
Evolocumab_Statin	0.52	[0.34; 0.79]	0.52
Ezetimibe_Statin	0.56	[0.42; 0.75]	0.45
IcosapentEthyl_Statin	0.39	[0.25; 0.62]	0.72
Probucol_Statin	0.84	[0.41; 1.75]	0.18
Statin	0.62	[0.52; 0.75]	0.31
Varespladib_Statin	0.66	[0.38; 1.14]	0.32



C

Comparison: other vs 'Control' (Random Effects Model)

Treatment	HR	95%–CI	SUCRA
Atorvastatin	0.76	[0.63; 0.90]	0.83
Control	1.00		0.15
EPA_pitavastatin	0.67	[0.47; 0.96]	0.91
Ezetimibe_pitavastatin	0.93	[0.76; 1.14]	0.33
Fluvastatin	0.90	[0.82; 0.98]	0.42
Pitavastatin	0.98	[0.81; 1.18]	0.20
Pravastatin	0.96	[0.73; 1.26]	0.29
Provastatin	0.84	[0.69; 1.02]	0.59
Varespladib_atorvastatin	0.77	[0.61; 0.97]	0.77

D

Comparison: other vs 'Control' (Random Effects Model)

Treatment	HR	95%–CI	SUCRA
Control	1.00		0.03
EPA_Statin	0.60	[0.42; 0.85]	0.96
Evolocumab_Statin	0.81	[0.69; 0.95]	0.57
Ezetimibe_Statin	0.83	[0.70; 0.98]	0.50
IcosapentEthyl_Statin	0.73	[0.62; 0.86]	0.81
Statin	0.87	[0.79; 0.97]	0.32
Varespladib_Statin	0.89	[0.72; 1.10]	0.31

E

Comparison: other vs 'Control' (Random Effects Model)

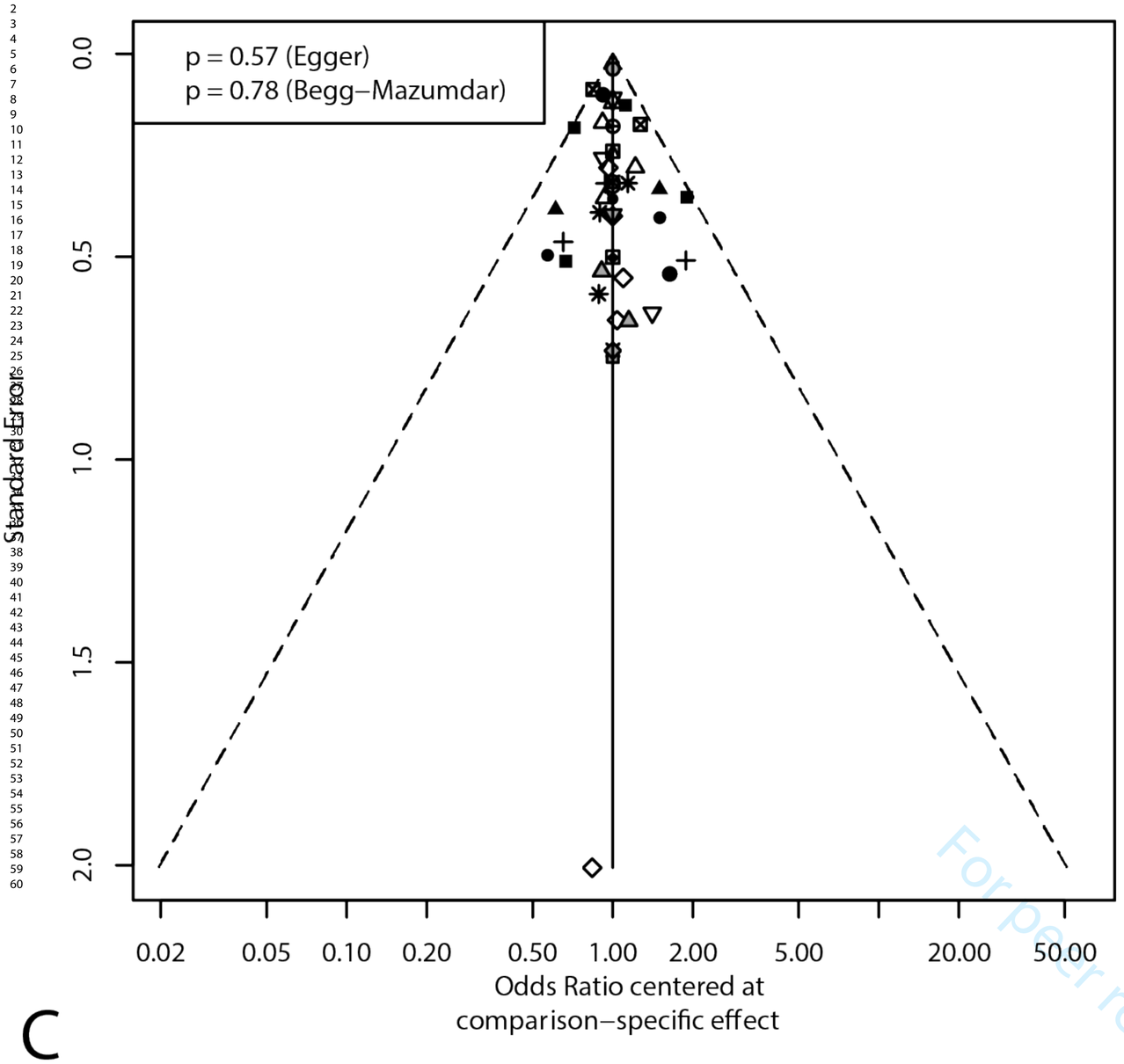
Treatment	OR	95%–CI	SUCRA
Alirocumab_rosuvastatin	0.52	[0.05; 5.09]	0.58
Atorvastatin	0.65	[0.40; 1.05]	0.56
Control	1.00		0.35
EPA_pitavastatin	0.48	[0.06; 3.56]	0.63
Evolocumab_atorvastatin_ezetimibe	1.79	[0.01; 294.47]	0.37
Evolocumab_pitavastatin	1.00	[0.06; 16.85]	0.41
Ezetimibe_atorvastatin	0.66	[0.01; 34.32]	0.51
Ezetimibe_pitavastatin	0.73	[0.14; 3.98]	0.50
Ezetimibe_rosuvastatin	0.14	[0.02; 1.26]	0.86
Fluvastatin	0.72	[0.47; 1.11]	0.49
Lovastatin	0.76	[0.18; 3.17]	0.47
Lovastatin_probucol	0.41	[0.04; 3.99]	0.63
Pitavastatin	1.04	[0.20; 5.39]	0.37
Pravastatin	1.13	[0.74; 1.72]	0.31
Provastatin	1.00	[0.52; 1.91]	0.36
Rosuvastatin	0.30	[0.11; 0.84]	0.79
Simvastatin	1.42	[0.10; 19.50]	0.32

F

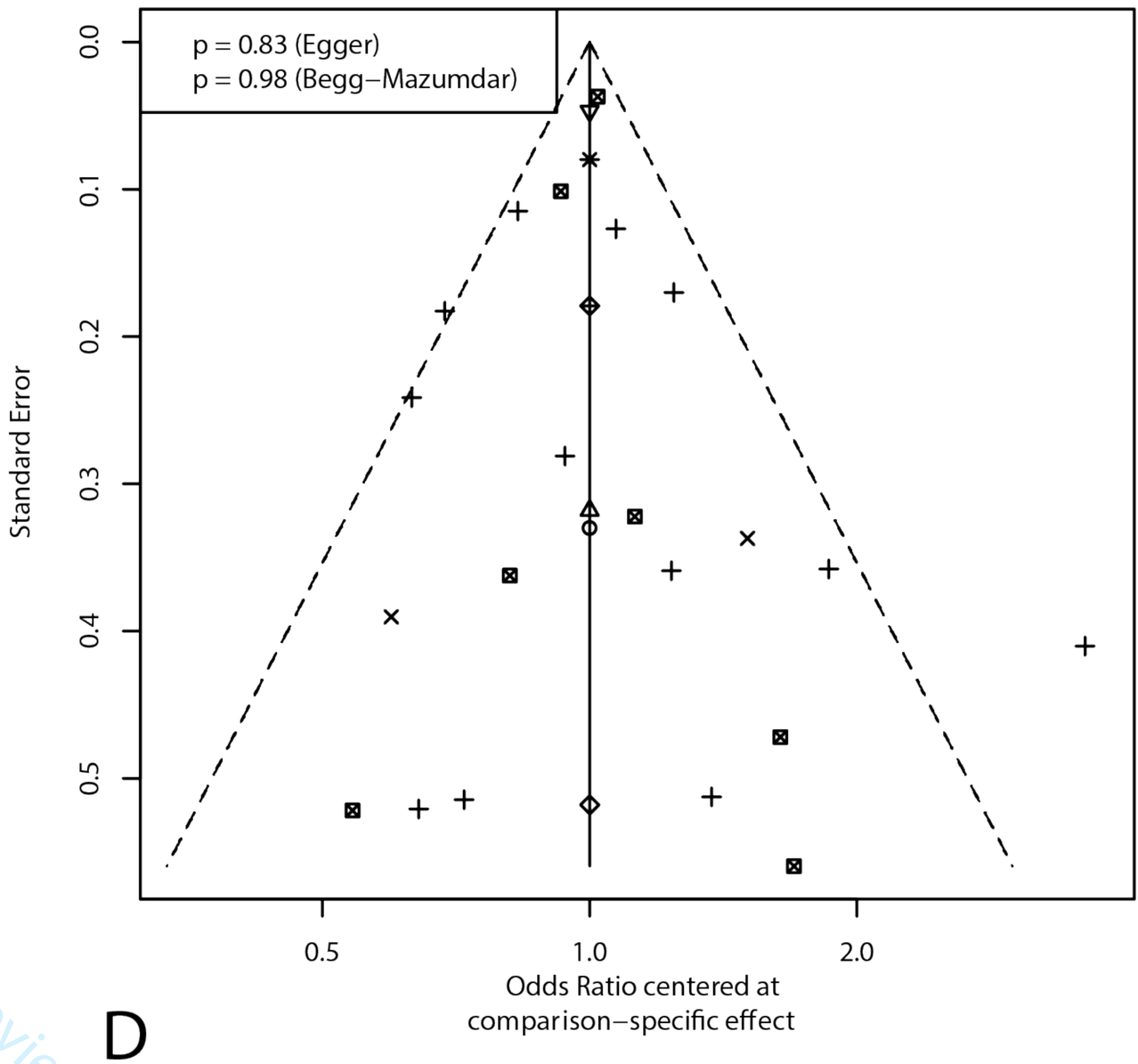
Comparison: other vs 'Control' (Random Effects Model)

Treatment	OR	95%–CI	SUCRA
Alirocumab_Statin	1.37	[0.18; 10.68]	0.27
Control	1.00		0.23
EPA_Statin	0.36	[0.11; 1.20]	0.82
Evolocumab_ezetimibe_Statin	1.51	[0.06; 39.09]	0.33
Evolocumab_Statin	0.91	[0.63; 1.30]	0.32
Ezetimibe_Statin	0.55	[0.34; 0.89]	0.75
IcosapentEthyl_Statin	0.66	[0.45; 0.96]	0.63
Probucol_Statin	0.41	[0.04; 3.99]	0.70
Statin	0.79	[0.61; 1.04]	0.46

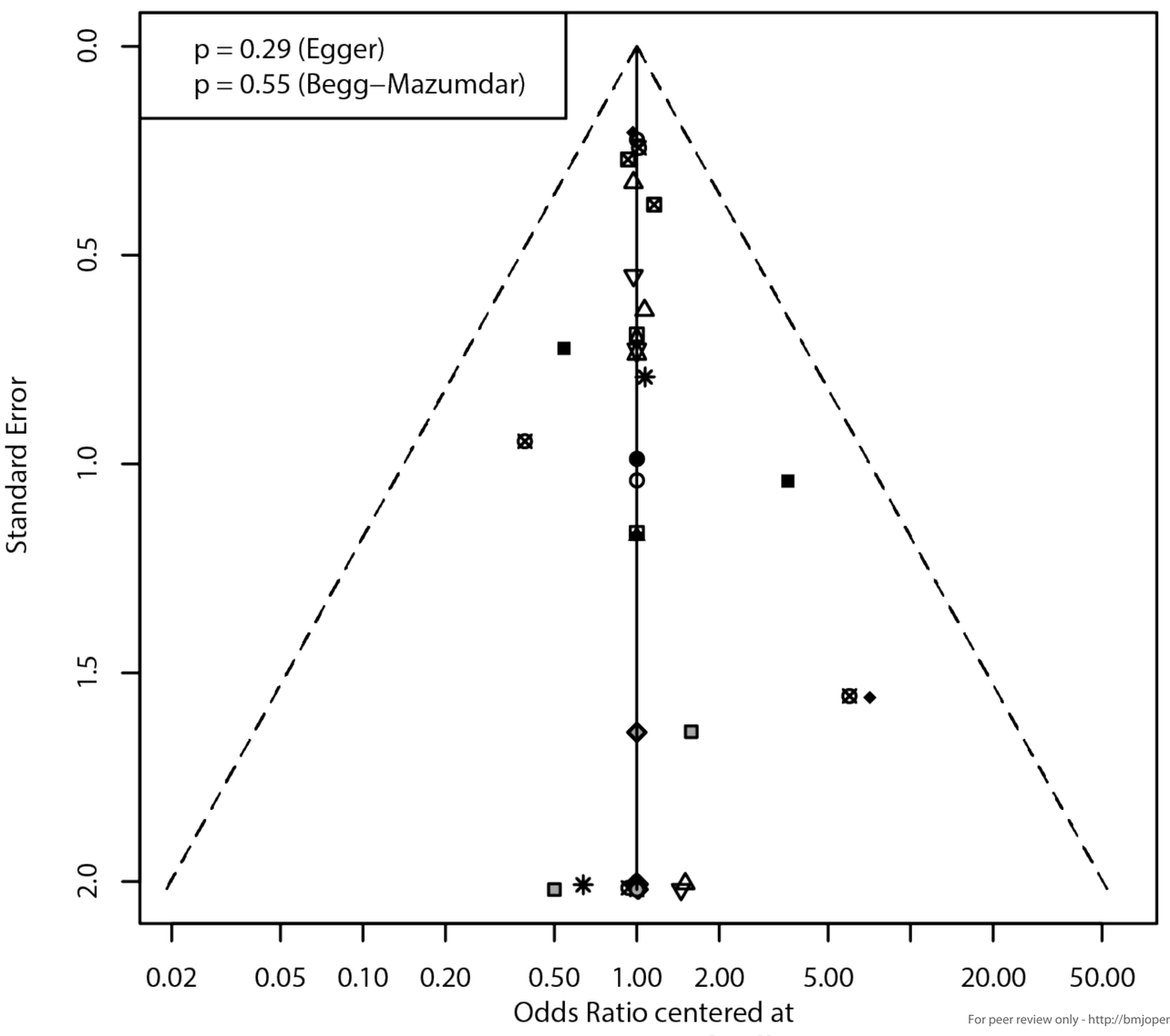
A



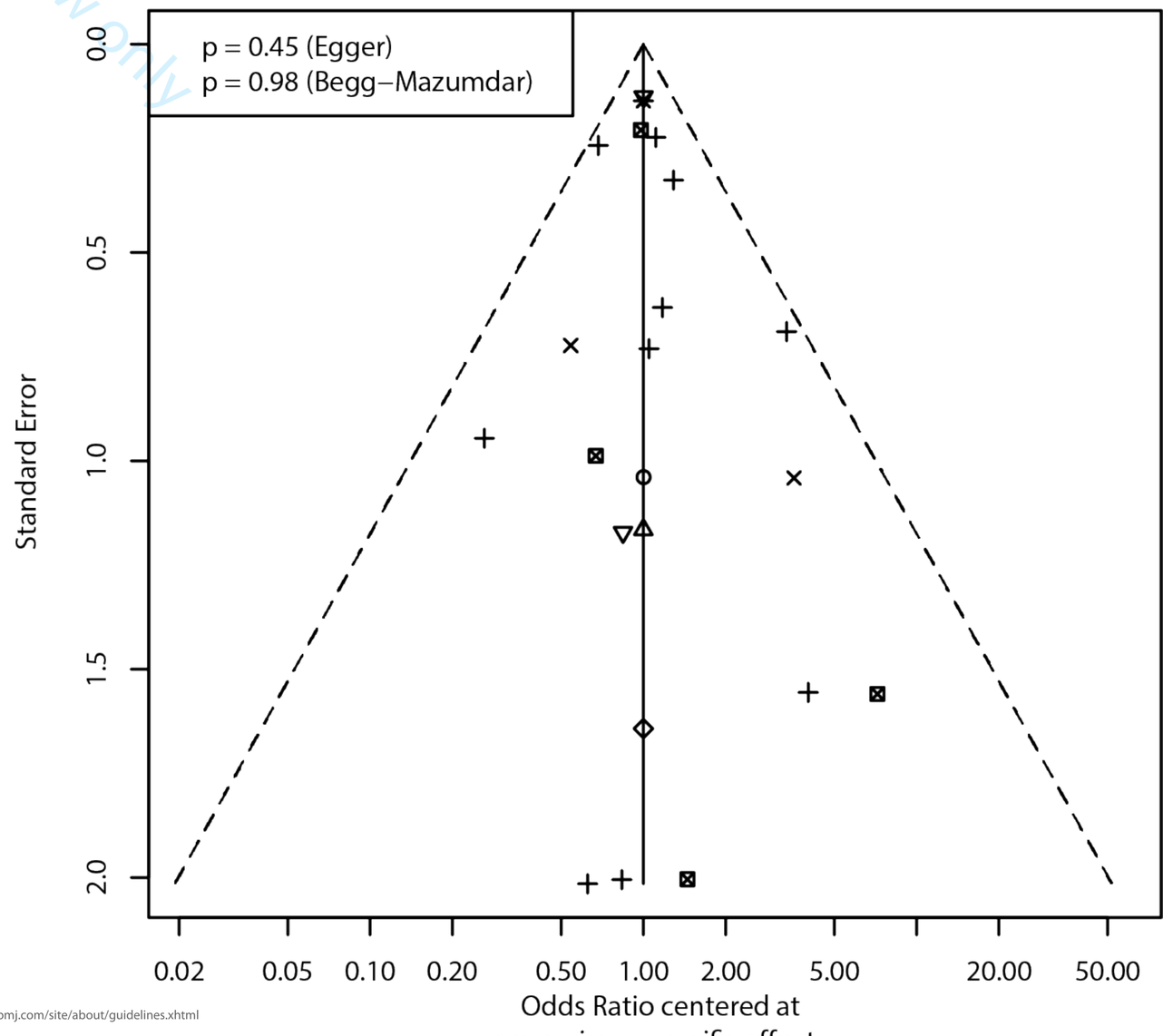
B



C



D



The full search strategy for all databases.

a. The search query used in PubMed database without language or other additional limits.

Search number	Query	Results
4	((#1) AND (#2)) AND (#3)	553
3	Random* or randomized or randomised	1,591,835
2	"percutaneous coronary intervention" OR "Coronary angioplasty"	61,003
1	Statin or Simvastatin or Rosuvastatin or Atorvastatin or Fluvastatin or Lovastatin or Pravastatin or Mevastatin or ezetimibe or "Icosapent Ethyl" or "Bempedoic acid" or fibrate or evolocumab or Alirocumab or evinacumab or Volanesorsen or Vupanorsen or Pelacarsen or Olezarsen or Pelacarsen or Inclisiran or olpasiran or Lipid-lowering	88,902

b. The search strategy used in EmBase database without language or other additional limits.

No.	Query	Results
#4	#1 AND #2 AND #3	1308
#3	random* OR randomized	2080906
#2	percutaneous coronary intervention' OR 'coronary angioplasty'	131280
#1	'statin'/exp OR statin OR 'simvastatin'/exp OR simvastatin OR 'rosuvastatin'/exp OR rosuvastatin OR 'atorvastatin'/exp OR atorvastatin OR 'fluvastatin'/exp OR fluvastatin OR 'lovastatin'/exp OR lovastatin OR 'pravastatin'/exp OR pravastatin OR 'pitavastatin'/exp OR pitavastatin OR 'mevastatin'/exp OR mevastatin OR 'ezetimibe'/exp OR ezetimibe OR 'eicosapentaenoic acid'/exp OR 'eicosapentaenoic acid' OR 'icosapent ethyl'/exp OR 'icosapent ethyl' OR 'bempedoic acid'/exp OR 'bempedoic acid' OR 'fibrate'/exp OR fibrate OR 'bezafibrate'/exp OR bezafibrate OR 'gemfibrozil'/exp OR gemfibrozil OR 'fenofibrate'/exp OR fenofibrate OR 'ciprofibrate'/exp OR ciprofibrate OR 'evolocumab'/exp OR evolocumab OR 'alirocumab'/exp OR alirocumab OR evinacumab OR 'volanesorsen'/exp OR volanesorsen OR 'vupanorsen'/exp OR vupanorsen OR 'pelacarsen'/exp OR pelacarsen OR 'olezarsen'/exp OR olezarsen OR 'inclisiran'/exp OR inclisiran OR 'olpasiran'/exp OR olpasiran OR 'lipid lowering'	167569

c. The search strategy used in Cochrane library database without language or other additional limits.

ID	Search	Hits

#1	(Statin OR Simvastatin OR Rosuvastatin OR Atorvastatin OR Fluvastatin OR Lovastatin OR Pravastatin OR Pitavastatin or Mevastatin OR ezetimibe OR "Eicosapentaenoic Acid" OR "Icosapent Ethyl" OR "Bempedoic acid" OR Fibrate OR Bezafibrate OR Gemfibrozil OR Fenofibrate OR Ciprofibrate OR Evolocumab OR Alirocumab OR Evinacumab OR Volanesorsen OR Vupanorsen OR Pelacarsen OR Olezarsen OR Inclisiran OR Olpasiran OR Lipid-lowering)	19395
#2	"Percutaneous coronary intervention" OR "Coronary angioplasty"	13623
#3	Random* OR randomized	1346916
#4	#1 AND #2 AND #3	690

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	***P.1***
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	P.2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	***P.3-P.4***
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	P.4
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	P.4- P.5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	***P.5-P.6***
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P.5
Search	8	Present full electronic search strategy for at least one	P.5

		database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P.5-P.6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P.6-P.7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P.6-P.7
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	***P.7***
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P.7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	P.7
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	P.7
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	P.7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**P.7**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	***n/a***

RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	P.8
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	***P.10-P.12***
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	***P.10-P.12***
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	P.9-P.10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	P.9-P.10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	***P.10-P.12***
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	***P.10-P.12***
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	***P.10-P.12***
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	P.10-P.12
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	***n/a***
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	P.12

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	P.15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P.16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	***P.16***

PICOS = population, intervention, comparators, outcomes, study design.

BMJ Open

Effectiveness of lipid-lowering therapy on mortality and major adverse cardiovascular event outcomes in patients undergoing percutaneous coronary intervention: a network meta-analysis of randomized controlled trials

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Effectiveness of lipid-lowering therapy on mortality and major adverse cardiovascular event outcomes in patients undergoing percutaneous coronary intervention: a network meta-analysis of randomized controlled trials

Chang-Jiang Deng[1], Ju Yan[2], Ying-Ying Zheng[1],Ting-Ting Wu[1], Ying Pan[1], Xian-Geng Hou[1],Si-Fan Wang[1], Subinur·Sirajidin[1], Mikereyi.Aimaitijiang[1],Xiang Xie[1]

1. Department of Cardiology, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, 830011, P.R. China.

2. Department of Cardiology, Shaanxi Provincial People's Hospital, Xi'an, 710000, P.R. China.

Correspondence authors:

Xiang Xie, No. 137, Liyushan Road, Department of Cardiology, First Affiliated Hospital of Xinjiang Medical University, Urumqi, 830011 P.R., China. Tel: +8609914366168; Email: xiangxie999@sina.com

Abstract

Background

Emergency percutaneous coronary intervention (PCI) can quickly restore myocardial perfusion after acute coronary syndrome (ACS). Whether and which lipid-lowering regimens are effective in reducing major adverse cardiovascular events (MACEs) and mortality risk after PCI remain unclear.

Objective

This study assessed the benefits of different lipid-lowering regimens on the risk of MACEs and mortality in the post-PCI population by network meta-analysis.

Methods

Public databases, including PubMed, Embase, and the Cochrane Library, were searched from inception to August 2022. Randomized controlled trials (RCTs) on lipid-lowering regimens in post-PCI populations were included and analysed. The outcomes were the incidence of all-cause mortality and MACEs, whether reported as dichotomous variables or as hazard ratios (HRs).

Results

Thirty-nine RCTs were included. For MACEs, alirocumab plus rosuvastatin (OR: 0.18; 95% CI: 0.07-0.44), evolocumab plus ezetimibe and statins (OR: 0.19; 95% CI: 0.06-0.59), eicosapentaenoic acid (EPA) plus pitavastatin (HR: 0.67; 95% CI: 0.49-0.96), and icosapent ethyl plus statins (HR: 0.73; 95% CI: 0.62-0.86) had significant advantages and relatively high rankings. For mortality, rosuvastatin (OR: 0.30; 95% CI: 0.11-0.84), ezetimibe plus statins (OR: 0.55; 95% CI: 0.43-0.89) and icosapent ethyl plus statins (OR: 0.66; 95% CI: 0.45-0.96) had significant advantages compared to the control.

Conclusion

EPA, especially icosapent ethyl, plus statins had a beneficial effect on reducing the risk of MACEs and mortality in post-PCI patients. PCSK9is plus statins were able to reduce the risk of MACEs, but the risk of mortality remained unclear.

Key words: lipid-lowering therapy, major adverse cardiovascular events, mortality,

network meta-analysis

Strengths and limitations of this study

- Only RCTs with high overall design quality were considered for inclusion.
- MACE and mortality were adopted as outcomes with little influence from subjective factors.
- this meta-analysis was based on the study level instead of the individual level.
- The criteria for defining MACEs varied among studies.
- Many included studies only reported dichotomous outcomes but did not report the HR results.

Introduction

Acute coronary syndrome (ACS) is a term used to refer to a range of conditions associated with acute myocardial ischaemia and/or infarction, which are usually due to coronary artery occlusion and acute ischaemic necrosis of the myocardium due to progression of coronary atherosclerotic lesions(1, 2). Emergency percutaneous coronary intervention (PCI) can quickly restore myocardial perfusion(3). Although the development of technological and procedural PCI has resulted in substantial improvements in clinical outcomes, recurrent coronary events may still occur after PCI(4).

The view of "residual cardiovascular risk" was introduced because MACEs still occurs in some patients who underwent PCI during follow-up. PCI can treat focal manifestations of systemic progressive disease, but the residual risk of acute coronary syndrome is largely related to the systemic proatherosclerotic effect of poorly

controlled cardiovascular risk factors(4). Lowering lipid levels, especially LDL-C, can halt the progression of coronary atherosclerosis and improve cardiovascular outcomes. Based on this view, it is believed that long-term optimal lipid-lowering therapy is effective in reducing long-term cardiovascular events after PCI. However, this view was still subject to challenges.

Based on data from the "Korea Acute Myocardial Infarction Registry", the proponents concluded that patients treated with statins had significantly lower rates of MACEs, all-cause death, and cardiac death during the 2-year follow-up period after PCI application(5). However, a study of postoperative follow-up of PCI patients enrolled in the Melbourne Interventional Group registry concluded that statins have no significant beneficial effect on MACEs after PCI(6). The controversy may be explained by two concepts: on the one hand, the optimal lipid reduction target may not be achieved by using single statins(7,8). On the other hand, long-term high-dose application of statins increases the risk of intracerebral haemorrhage and other side effects(9,10).

There is a consensus on preloading high-dose statins to reduce MACEs in the perioperative period with PCI(11,12). However, there is still insufficient evidence for the continued application of lipid-lowering drugs to reduce the risk of long-term MACEs and mortality. This study assessed the benefits of different lipid-lowering regimens on the risk of MACEs and mortality in the post-PCI population by network

meta-analysis.

Methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study was registered with PROSPERO (CRD 42018099600).

Patient and Public Involvement

None

Search strategy

Public literature databases, including PubMed, Embase, and the Cochrane Library, were searched from inception to August 2022 without language restrictions using the following search terms: (lipid-lowering or statin or simvastatin or rosuvastatin or atorvastatin or fluvastatin or lovastatin or pravastatin or pitavastatin or mevastatin or ezetimibe or “eicosapentaenoic acid” or “icosapent ethyl” or “bempedoic acid” or fibrate or bezafibrate or gemfibrozil or fenofibrate or ciprofibrate or evolocumab or alirocumab or evinacumab or volanesorsen or vupanorsen or pelacarsen or olezarsen or inclisiran or olpasiran) and (“percutaneous coronary intervention” or “coronary angioplasty”) and (random* or randomized or randomized). The details of the full search strategy are listed in the Supplementary file. The references of relevant systematic reviews and meta-analyses were also searched to avoid omissions. The two authors conducted literature retrieval independently, and any conflicts were resolved

through discussion with the third author.

Inclusion and exclusion criteria

The literature was included if it met the following criteria: 1) the study adopted a randomized controlled study design; 2) the study included patients who underwent PCI surgery or reported the subgroup of the population that underwent PCI; 3) the lipid-lowering regimen was applied to the population of the intervention group; 4) the control group used a different lipid-lowering agent or regimen; and 5) the study reported the outcome of mortality and/or MACEs. The exclusion criteria were as follows: 1) as preloading of statins before PCI was shown to have clear benefits, to determine whether application of lipid-lowering drugs after PCI also had beneficial effects, this work excluded studies on the preloading application of lipid-lowering drugs before PCI; and 2) although high-dose lipid-lowering agents, such as statins, have a better lipid-lowering effect, long-term application may bring potential side effects(9,13). Therefore, only studies in which all agents were considered to be applied at reasonable doses were included, and dose–response studies were excluded. In addition, repeatedly published studies, protocols, conference abstracts, reviews, comments and editorials were also excluded.

Data extraction and quality assessment

Two authors independently extracted the information from the included studies. The contents include the name of the first author, publication year, study location, sample

size (population that underwent PCI), study abbreviation and registration number, lipid-lowering intervention and control, and follow-up time.

The outcomes analysed were the incidence of all-cause mortality and MACEs, whether reported as dichotomous or hazard ratio (HR) statistics based on Cox regression. The MACE outcome was selected to most closely approximate the composite endpoint, including mortality, MI, stroke, coronary revascularization, and restenosis. Study quality was assessed by two investigators using the Cochrane risk of bias assessment tool, which included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential biases.

Statistical analysis

We conducted frequentist network meta-analysis (NMA) using random-effects models weighted by the inverse variance method. Odds ratios (ORs) and 95% confidence intervals (CIs) were used for dichotomous outcomes. The hazard ratios (HRs) and 95% CIs based on Cox regression results were also pooled for reporting. If the HR value was not reported but there was a Kaplan–Meier survival curve, the HR value was extracted from the curve by GetData Graph Digitizer software version 2.24. In network plots, the direct comparisons among treatment arms are shown, the end of each line indicates a treatment arm, and the thickness of the lines indicates the number of studies comparing the two treatments. Forest plots were used to describe the

network comparison results between each treatment and the control.

The restricted maximum likelihood estimation was used to quantify network heterogeneity. The Q statistic was used to assess the sum of statistics for heterogeneity (within designs) and for overall inconsistency (between designs)(14). The ranking probabilities of each regimen were estimated using the surface under the cumulative ranking curve (SUCRA), which was the ratio of the area under the curve to the entire area. A comparison-adjusted funnel plot was used to examine potential publication biases in the NMA. P values of less than 0.05 were considered to indicate statistical significance. The NMA was performed using R language with the "netmeta" package.

Results

After removing duplicates, we obtained 1588 literature items. After screening the titles and abstracts, 1515 irrelevant studies were excluded. Seventy-three articles were screened for full text. The following articles were excluded: dose–response studies (8); those where no PCI population or subgroup was reported (6); those where no mortality or MACE-related outcomes were reported (6); repeated publications (5); studies related to preloading of lipid-lowering agents (4); studies unrelated to lipid-lowering agents (3); a protocol study (1); and a study with a non-RCT design (1). Finally, 39 articles were included, containing 54478 post-PCI patients (15-53) (Figure 1).

Table 1. The characteristics of included studies

Study	Location	Sample size	Abbreviation	Register ID	Intervention	Control	Follow-up#
Lorenz Räber 2022 [15]	European	300	PACMAN-AMI	NCT03067844	Alirocumab;rosuvastatin	Placebo;rosuvastatin	52W
Peterson, B. E. 2022 [16]	Multicenter	3408	REDUCE-IT PCI	NCT01492361	Icosapent ethyl;statins	Placebo;statins	4.8Y
Remo H.M. Furtado 2022 [17]	Multicenter	17073	FOURIER	NCT01764633	Evolocumab;statins	Placebo;statins	2.2Y
Tomoaki Okada 2022 [18]	Japan	102	-	UMIN000028729	Evolocumab;pitavastatin	Pitavastatin	4W
Yan Hao 2022 [19]	China	136	-	-	Evolocumab;atorvastatin;ezetimibe	Ezetimibe;atorvastatin	3M
Deng YF 2021 [20]	China	90	-	-	Ezetimibe;atorvastatin	Atorvastatin	1Y
Sun C 2021 [21]	China	171	-	ChiCTR-IPR-17012219	Ezetimibe;rosuvastatin	Rosuvastatin	3M
Weifeng He 2020 [22]	China	192	-	-	Atorvastatin vs. Rosuvastatin vs. Simvastatin	-	6M
Kiyoshi Hibi 2018 [23]	Japan	128	Ezetimibe-ACS	NCT00549926	Ezetimibe;pitavastatin	Pitavastatin	1Y
Eui Im 2017 [24]	Korea	2000		NCT01557075	Atorvastatin	Pravastatin	1Y
Hagiwara N 2017 [25]	Japan	1734	HIJ-PROPER	UMIN000002742	Ezetimibe;pitavastatin	Pitavastatin	36M
J Guo 2017 [26]	China	137	-	-	Rosuvastatin	Control	1Y
Wang YB 2017 [27]	China	132	-	ChiCTR-IPR-15007035	Pitavastatin	Atorvastatin	6M
Watanabe T 2017 [28]	Japan	193	CHERRY	UMIN000002815	EPA;pitavastatin	Pitavastatin	6-8M
Zhi Liu 2017 [29]	China	102	-	-	Ezetimibe;atorvastatin	atorvastatin 20mg/d	1Y
Kazumasa Nosaka 2016 [30]	Japan	241	-	UMIN000016723	EPA;pitavastatin	Pitavastatin	1Y
Kensuke Matsushita 2016 [31]	Japan	118	Yokohama-ACS	NCT00549926	Atorvastatin vs. Pitavastatin vs. Pravastatin vs. Fluvastatin	-	10.3M
Christopher P Cannon 2015 [32]	Multicenter	12941	IMPROVE-IT	NCT00202878	Ezetimibe;simvastatin	Simvastatin	6M
Kenichi Tsujita 2015 [33]	Multicenter	246	PRECISE-IVUS	NCT01043380	Ezetimibe;atorvastatin	Atorvastatin	1Y
Stephen J. Nicholls 2015 [34]	Multicenter	3295	VISTA-16	NCT01130246	Varespladib;atorvastatin	Placebo;atorvastatin	6M
Zhang JR 2015 [35]	China	104	-	-	Atorvastatin	Rosuvastatin	6M
Mario Leoncin 2014 [36]	Italy	333	PRATO-ACS	NCT01185938	Rosuvastatin	Control	6M
Hiroyuki Takano 2013 [37]	Japan	458	PEARL	UMINC000000428	Pitavastatin	Control	35.5M
Tsuyoshi Nozue 2013 [38]	Japan	164	TRUTH	UMIN000004627	Pitavastatin	Pravastatin	2Y
Jean-Marc Lablanche 2010 [39]	Multicenter	887	CENTAURUS	NCT00296387	Rosuvastatin	Atorvastatin	3M
C. Michael Gibson 2009 [40]	US	2868	PROVE IT-TIMI 22	NCT00382460	Atorvastatin	Provastatin	2Y
Han Yaling 2009 [41]	China	1275	-	NCT00405717	Atorvastatin	Provastatin	1Y

Takafumi Hiro 2009 [42]	Japan	307	JAPAN-ACS	NCT00242944	Pitavastatin	Atorvastatin	1Y
Tomotaka Dohi 2009 [43]	Japan	180	Extended-ESTABLISH trial	-	Atorvastatin	Control	4Y
Toru Toi 2009 [44]	Japan	160	-	-	Pitavastatin	Atorvastatin	17D
Xu Kai 2007 [45]	China	648	-	-	Atorvastatin	Control	2Y
Bae JH 2004 [46]	Korea	205	-	-	Atorvastatin	Control	6M
Patrick W J C Serruys 2002 [47]	Multicenter	1677	LIPS	-	Fluvastatin	Placebo	3.9Y
Han J.G.H. Mulder 2000 [48]	Netherland	201	REGRESS	-	Pravastatin	Placebo	2Y
Greg C. Flaker 1999 [49]	Multicenter	1154	CARE trial	-	Pravastatin	Placebo	6Y
MICHEL E. BERTRAND 1997 [50]	France	695	PREDICT	-	Pravastatin	Placebo	6M
J H O'Keefe Jr 1996 [51]	US	200	APPLE	-	Probucol;lovastatin	Placebo	6M
Haruhiko Onaka 1994 [52]	Japan	66	-	-	Pravastatin	Control	5M
Rakesh Sahni 1991 [53]	US	157	-	-	Lovastatin	Control	6M

Abbreviations: EPA: eicosapentaenoic acid.

#: Follow-up period: Y: years; M: months; W: weeks; D: days

Among the included studies, the publication period ranged from 1991 to 2022. The research locations were mainly in Asia (China, Japan and South Korea), Europe (Netherlands, France, and Italy), America, and multiple centres. There were 10 studies with sample sizes greater than 1000 patients. There were also 22 studies with publicly available clinical study registration numbers (Table 1). In terms of design quality, all included studies were RCTs. Therefore, the design quality was generally high. The main factors potentially affecting design quality were the blinding of participants and personnel and blinding of outcome assessment (Figure 2). However, as the desired outcomes were mortality and MACEs, the subjective factors of the investigator had little influence on the outcomes.

As two studies did not specify the types of statins, the network meta-analysis was divided into two parts. One part was analysed based on specific types of statins, and

the other was based on taking statins as a whole. For the dichotomous results of MACEs, the NMA based on specific types of statins included 18 lipid-lowering regimens. The Q test for heterogeneity (p = 0.07) and inconsistency (p = 0.16) were nonsignificant, indicating no evidence of heterogeneity or inconsistency in the NMA.

In pairwise comparisons with the control, alirocumab plus rosuvastatin (OR: 0.18; 95% CI: 0.07-0.44; SUCRA: 0.94), evolutionab plus atorvastatin and ezetimibe (OR: 0.18; 95% CI: 0.05-0.63; SUCRA: 0.90), and ezetimibe plus rosuvastatin (OR: 0.29; 95% CI: 0.11-0.76; SUCRA: 0.80) had significant advantages and relatively high SUCRA rankings. No potential publication bias was found according to the comparison-adjusted funnel plot (Figure 3).

In the NMA based on taking statins as a whole, ten regimens were analysed. Evolocumab plus ezetimibe and statins (OR: 0.19; 95% CI: 0.06-0.59; SUCRA: 0.92), alirocumab plus statins (OR: 0.27; 95% CI: 0.13-0.59; SUCRA: 0.87), and icosapent ethyl plus statins (OR: 0.39; 95% CI: 0.25-0.62; SUCRA: 0.72) had significant advantages and relatively high SUCRA rankings. No potential publication bias was found.

For the HR results of MACEs, the NMA based on specific types of statins included nine regimens. The Q test for heterogeneity was nonsignificant (p = 0.964) because the network comparisons lacked loops. Therefore, the results were considered consistent. Compared to the control, eicosapentaenoic acid (EPA) plus pitavastatin

(HR: 0.67; 95% CI: 0.49-0.96; SUCRA: 0.91), atorvastatin (HR: 0.76; 95% CI: 0.63-0.90; SUCRA: 0.83), and varespladib plus atorvastatin (HR: 0.77; 95% CI: 0.61-0.97; SUCRA: 0.77) had significant advantages and relatively high SUCRA rankings. Potential publication bias was not analysed due to the small number of included studies.

In the NMA based on taking statins as a whole, seven regimens were analysed. EPA plus statins (HR: 0.60; 95% CI: 0.42-0.85; SUCRA: 0.96) and icosapent ethyl plus statins (HR: 0.73; 95% CI: 0.62-0.86; SUCRA: 0.81) had significant advantages over the control.

For the dichotomous mortality results, the NMA based on specific types of statins included 17 lipid-lowering regimens. The Q test for heterogeneity ($p = 0.78$) and inconsistency ($p = 0.99$) were nonsignificant. Due to the rare occurrence of events, the results of the comparison had low precision with a large standard error. Compared to the control, only rosuvastatin (OR: 0.30; 95% CI: 0.11-0.84; SUCRA: 0.79) showed a significantly better effect. Ezetimibe plus rosuvastatin had a relatively high SUCRA ranking, but there was no significant difference compared to the control (OR: 0.14; 95% CI: 0.02-1.26; SUCRA: 0.86). No potential publication bias was found (Figure 4).

In the NMA based on taking statins as a whole, nine regimens were analysed.

Ezetimibe plus statins (OR: 0.55; 95% CI: 0.43-0.89; SUCRA: 0.75) and icosapent ethyl plus statins (OR: 0.66; 95% CI: 0.45-0.96; SUCRA: 0.63) had significant advantages compared with the blank control group. No potential publication bias existed. NMA analysis was not performed due to the small number of studies reporting HRs for mortality (Figure 5).

Discussion

This study analysed the benefits of lipid-lowering therapy on mortality and MACE outcomes in patients who underwent PCI by network meta-analysis. The results showed that several lipid-lowering regimens could reduce the risk of MACEs compared with the blank control. Icosapent ethyl plus statins had the benefit of reducing both the risk of MACEs and mortality. However, EPA plus statins had more advantages in reducing the risk of MACEs. Of note, based on the current evidence, alirocumab and evolocumab plus statins had obvious advantages in reducing the risk of MACEs but had no obvious benefit in reducing the risk of mortality.

EPA is a long-chain omega-3 polyunsaturated fatty acid. Long-term intake of EPA can reduce the residual cardiovascular risk to reduce the risk of MACEs(54). In terms of pathological mechanisms, EPA combined with pitavastatin was shown to reduce the lipid volume of coronary artery plaques and total atherosclerotic plaque volume in patients who underwent PCI, which may be the reason for the reduced risk of MACEs(55).

Icosapent ethyl is a highly purified and stable eicosapentaenoic acid ethyl ester that has potential higher anti-inflammatory, antioxidant, plaque stability and cell membrane stability effects(56). In the NMA results, icosapent ethyl plus statins had significant benefits for reducing the risk of either mortality or MACEs in patients who underwent PCI, which was an ideal regimen for the population.

Ezetimibe inhibits the absorption of cholesterol and has a synergistic lipid-lowering pharmacological effect with statins to further reduce the risk of death and MACEs. In particular, when combined with rosuvastatin, ezetimibe has a stronger lipid-lowering effect with a high safety profile without the risk of drug interactions(57). Our NMA results also showed that ezetimibe can reduce the risk of MACEs and mortality. According to the guidelines for the management of dyslipidaemia from the European Society of Cardiology and the European Atherosclerosis Society, ezetimibe was recommended if the LDL-C target was not reached(58,59). The American College of Cardiology guidelines also recommend adding ezetimibe when using maximally tolerated statin therapy and if LDL-C levels remained ≥ 70 mg/dL(60). These benefits have also been demonstrated in the secondary prevention of PCI.

Alirocumab and evolocumab are both proprotein convertase subtilisin/kexin type-9 inhibitors (PCSK9is), which can increase the level of LDL receptor in the liver, thus improving the ability of the liver to bind LDL-C and reducing the level of peripheral

LDL-C(61). There was also a synergistic lipid-lowering pharmacological effect when PCSK9is were combined with statins that resulted in a significantly reduced LDL-C concentration and atherosclerosis event risk; however, there was still controversy regarding the mortality risk reduction(62). It has been suggested that the powerful effect of PCSK9is on reducing LDL-C predisposes patients to hypocholesterolaemia, which will not increase the risk of cerebral haemorrhage. PCSK9is may be the preferred lipid-lowering agents in patients with elevated ICH risk (63-65). On the other hand, PCSK9is did not reduce serum inflammatory factors in one study, suggesting that they may not reduce the risk of residual inflammation in the post-PCI population(66).

In the results of this study, lipid-lowering therapy strategies had general advantages in reducing MACE risk. However, for all-cause mortality, the advantage of lipid-lowering therapy was not obvious. Based on dichotomous outcomes of mortality, some strategies may even have a tendency to increase the mortality risk. This challenges the opinion that lipid-lowering therapy is recommended after PCI(67). A large sample size retrospective study suggests that statins can reduce the risk of all-cause death in patients with coronary artery disease undergoing PCI, regardless of individual cholesterol levels(68). Alternatively, the “lipid paradox” view has been proposed and indicates that higher levels of LDL-C and triglycerides on admission are associated with better clinical outcomes. Especially in patients with ST-elevation myocardial infarction, lower LDL-C levels were associated with worse mortality

outcomes(69). However, this view is also controversial(70).

On the other hand, it is possible that the contribution of LDL-C reduction to the risk of mortality outcomes is obscured by other confounding factors. For example, inflammatory status may also have had an important impact on patient mortality risk. In a cohort of post-PCI patients with low LDL-C levels, residual inflammatory risk also had a significant effect on overall mortality(71). C-reactive protein can also predict long-term mortality in post-PCI patients independent of LDL-C levels(72). In addition, cardiac remodelling also has an important impact on the survival outcome of post-PCI patients(73).

There are several limitations in this study. First, this analysis was based on the study level instead of the individual level, making it difficult to consider the individual confounding factors in the analysis. Second, two included studies did not specify the type of statins, so our study had to be analysed separately according to whether all statins were considered as a whole. Third, the criteria for defining MACEs varied among studies, which contributed to heterogeneity among the study results. Fourth, many included studies only reported dichotomous outcomes but did not report the HR results, resulting in missing relevant data for the analysis.

In conclusion, the results of this study suggested that EPA, especially icosapent ethyl, plus statins had a beneficial effect on reducing the risk of MACEs and mortality in

post-PCI patients. PCSK9is plus statins were able to reduce the risk of MACEs, but the effects on the risk of mortality remained unclear.

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Author contributions

Chang-Jiang Deng completed the manuscript, Ju Yan, Ting-Ting Wu,Ying Pan,Ying-Ying Zheng guided the data analysis and the production of the figures, Xian-Geng Hou,Si-Fan Wang, Subinur·Sirajidin, Mikereyi.Aimaitijiang,Xiang Xie read and approved the fnal manuscript.

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Declarations

Ethics approval and consent to participate

This study does not involve human participants and ethical approval was not required.

Consent for publication

not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figure 1. Flowchart of the study selection process for eligible studies

Figure 2. Methodological quality assessment of included studies

Figure 3. Network plots of comparisons for major outcomes included in the analyses. A: dichotomous results of MACE based on specific types of statins; B: dichotomous results of MACE based on taking statins as a whole; C: hazard ratio results of MACE based on specific types of statins; D: hazard ratio results of MACE based on taking statins as a whole; E: dichotomous results of mortality based on specific types of statins; F: dichotomous results of mortality based on taking statins as a whole.

Figure 4. Forest plots of lipid-lowering therapy compare to control for outcomes in network meta-analysis with SUCRA ranking results. A: dichotomous results of MACE based on specific types of statins; B: dichotomous results of MACE based on taking statins as a whole; C: hazard ratio results of MACE based on specific types of statins; D: hazard ratio results of MACE based on taking statins as a whole; E: dichotomous results of mortality based on specific types of statins; F: dichotomous results of mortality based on taking statins as a whole.

Figure 5. The comparison-adjusted funnel plot for assessing all main outcomes. A: dichotomous results of MACE based on specific types of statins; B: dichotomous results of MACE based on taking statins as a whole; C: dichotomous results of

mortality based on specific types of statins; D: dichotomous results of mortality based on taking statins as a whole.

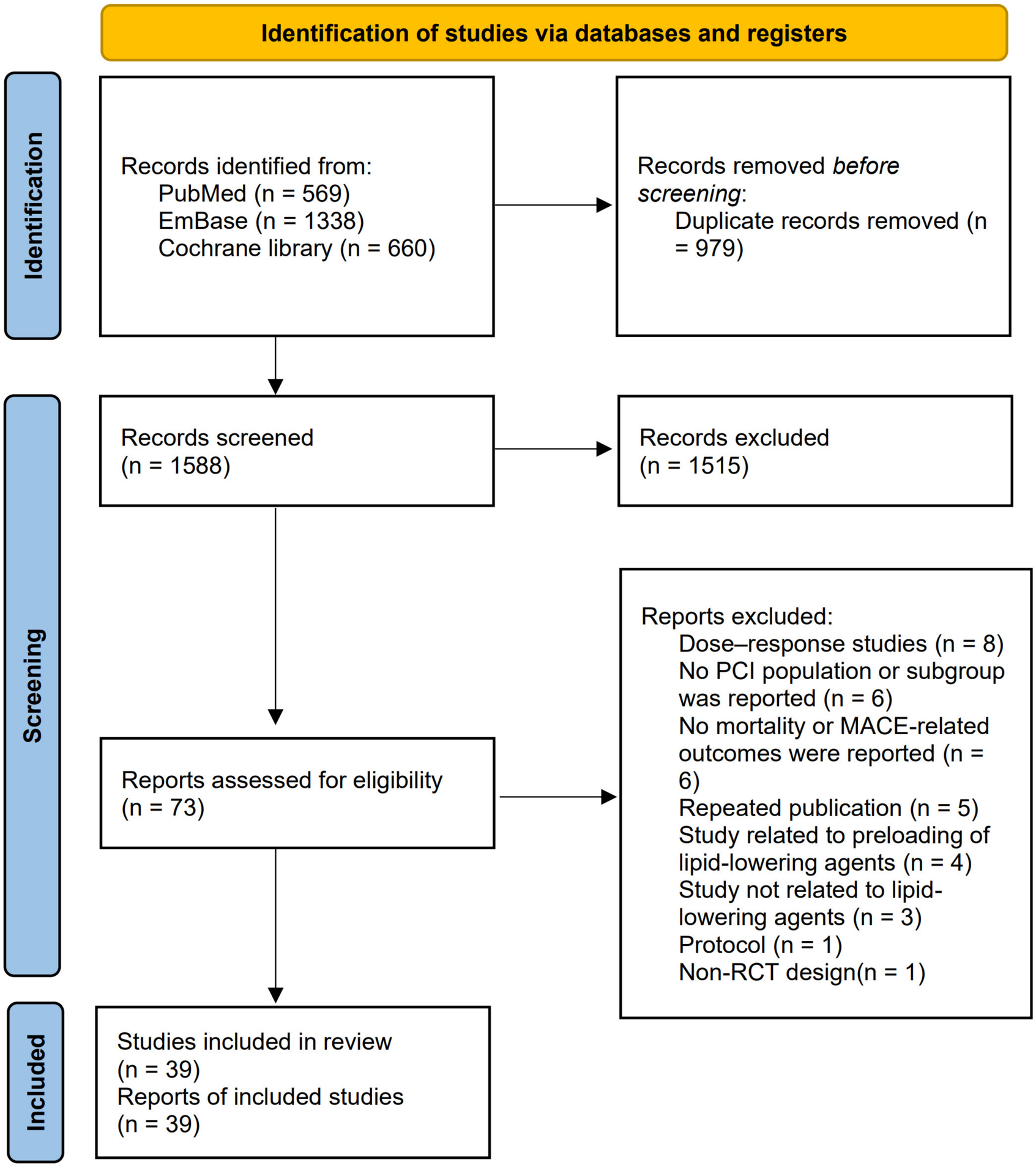
Authors and Afliations

Chang-Jiang Deng, Ju Yan, Ying-Ying Zheng,Ting-Ting Wu, Ying Pan, Xian-Geng Hou,Si-Fan Wang, Subinur·Sirajidin, Mikereyi·**Sirajidin**,Xiang Xie

Chang-Jiang Deng	Xian-Geng Hou
1187229853@qq.com	380138554@qq.com
Ju Yan	Si-Fan Wang
yyjj2017@163.com	562654119@qq.com
Ying-Ying Zheng	Subinur·Sirajidin
zhengying527@163.com	496568064@qq.com
Ting-TingWu	Mikereyi·Aimaitijiang
1255723526@qq.com	3195676352@qq.com
Ying Pan	Xiang Xie
2475854195@qq.com	xiangxie999@sina.com

Department of Cardiology, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, 830011, P.R. China.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

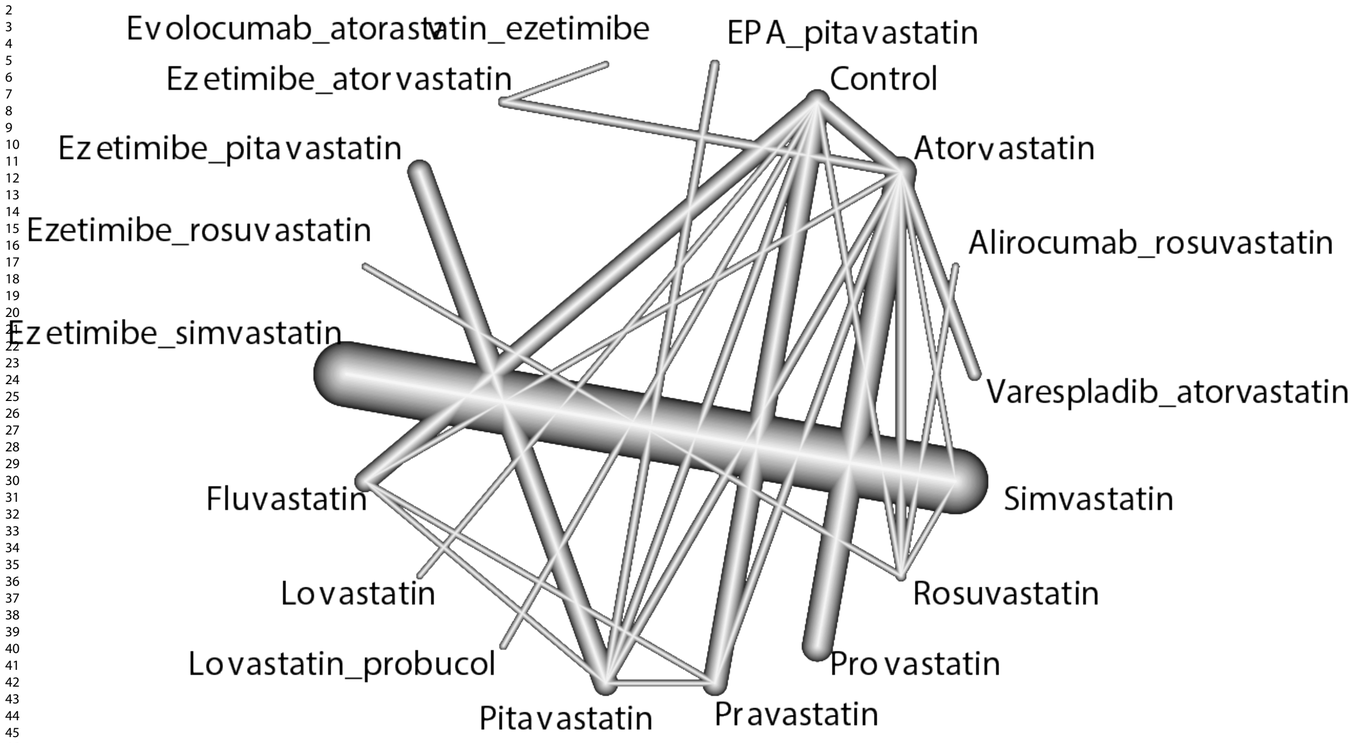
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Bae JH 2004
C. Michael Gibson 2009
Christopher P Cannon 2015
Deng YF 2021
Eui Im 2017
Greg C. Flaker 1999
Hagiwara N 2017
Han J.G.H. Mulder 2000
Han Yaling 2009
Haruhiko Onaka 1994
Hiroyuki Takano 2013
Jean-Marc Lablanche 2010
J Guo 2017
J H O'Keefe Jr 1996
Kazumasa Nosaka 2016
Kenichi Tsujita 2015
Kensuke Matsushita 2016
Kiyoshi Hibi 2018
Lorenz Räber 2022
Mario Leoncin 2014
MICHEL E. BERTRAND 1997
Patrick W J C Serruys 2002
Peterson, B. E. 2022
Rakesh Sahni 1991
Remo H.M. Furtado 2022
Stephen J. Nicholls 2015
Sun C 2021
Takafumi Hiro 2009
Tomoaki Okada 2022
Tomotaka Dohi 2009
Toru Toi 2009
Tsuyoshi Nozue 2013
Wang YB 2017
Watanabe T 2017
Weifeng He 2020
Xu Kai 2007
Yan Hao 2022
Zhang JR 2015
Zhi Liu 2017

A



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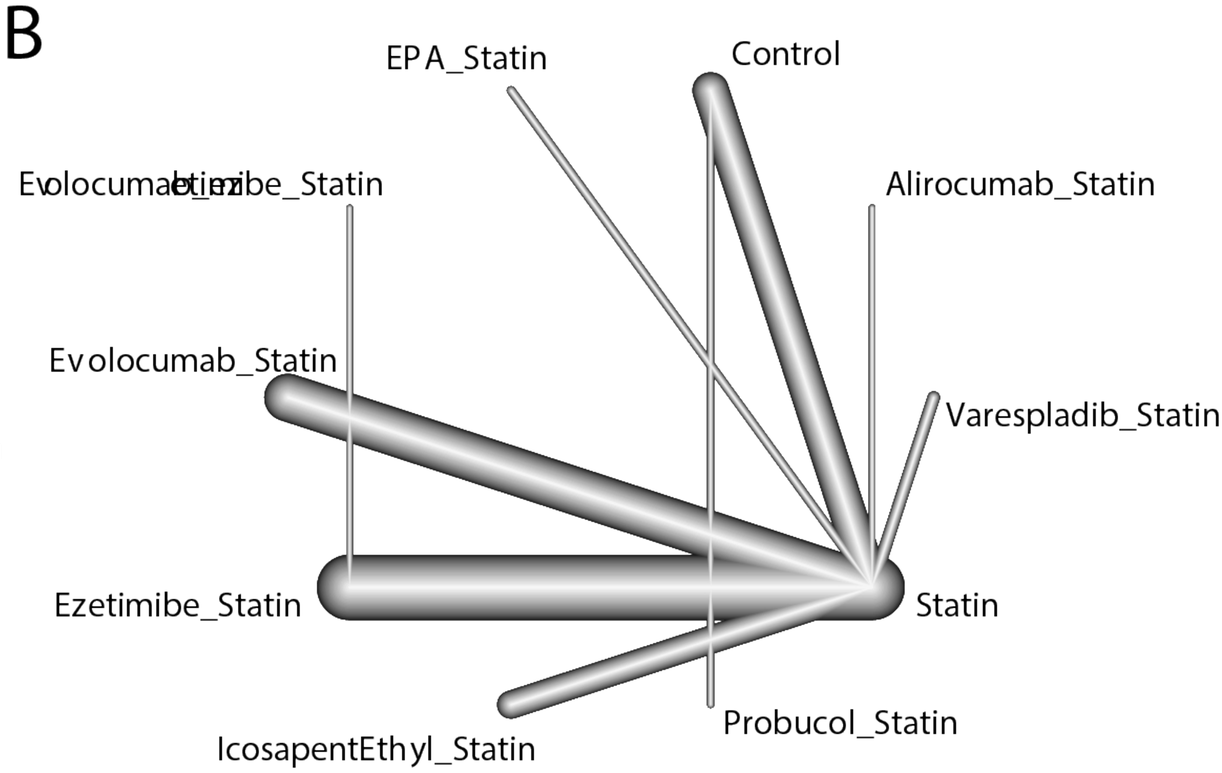

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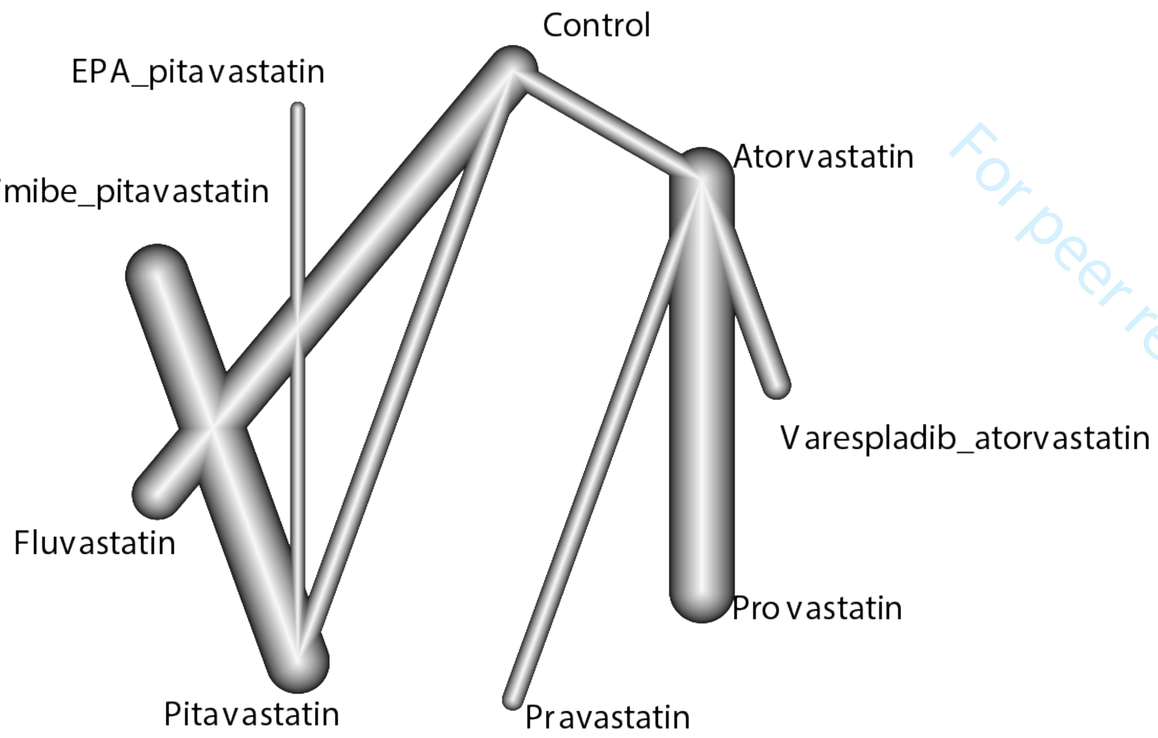

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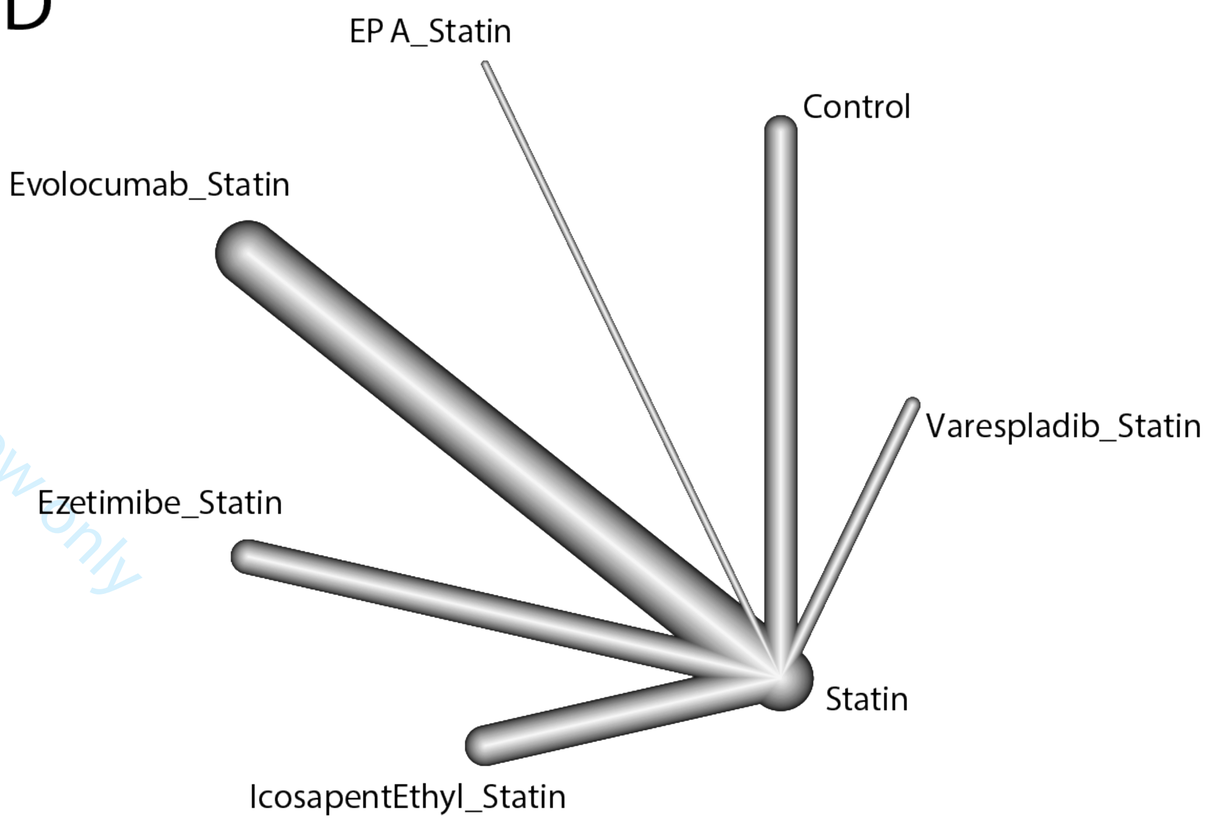

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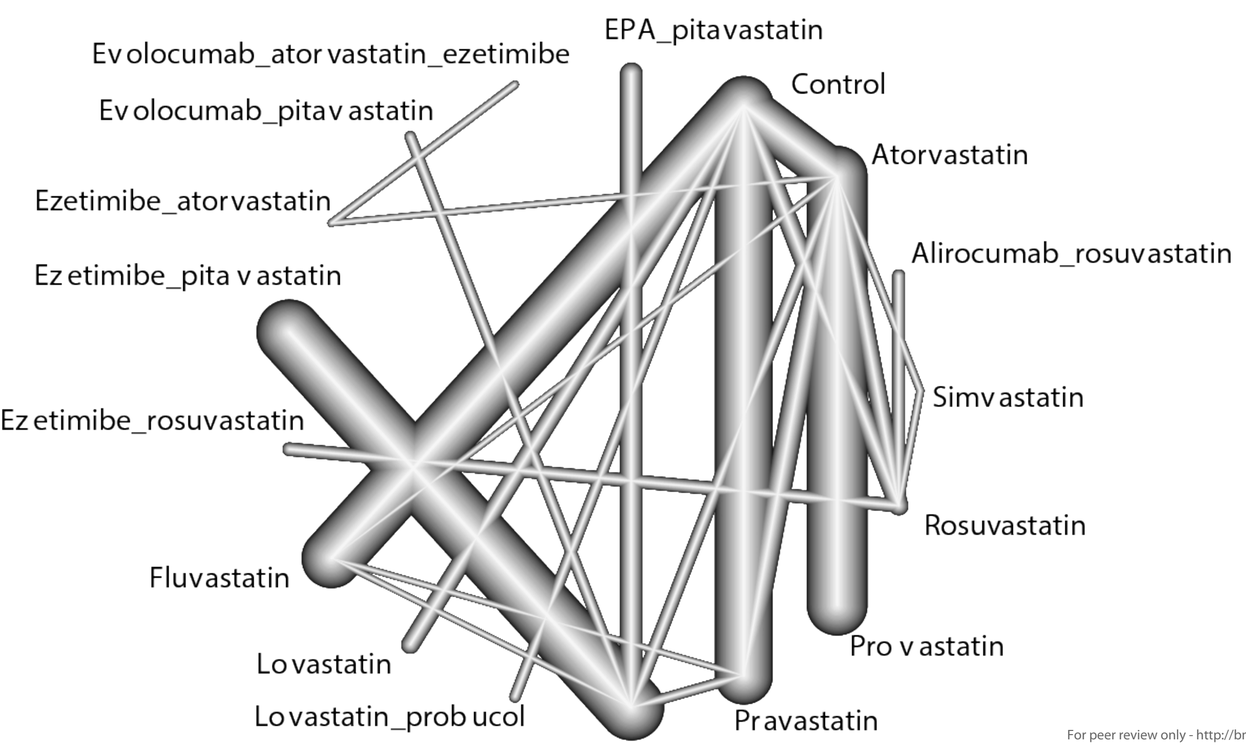

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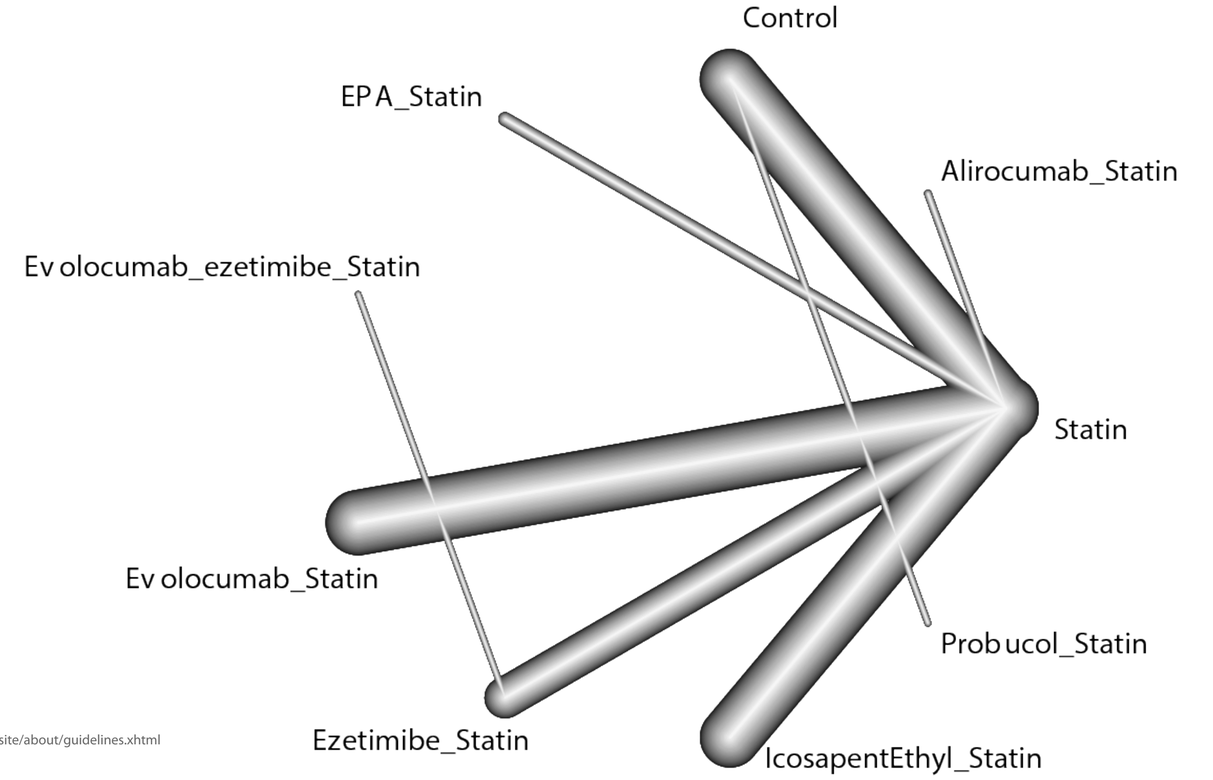

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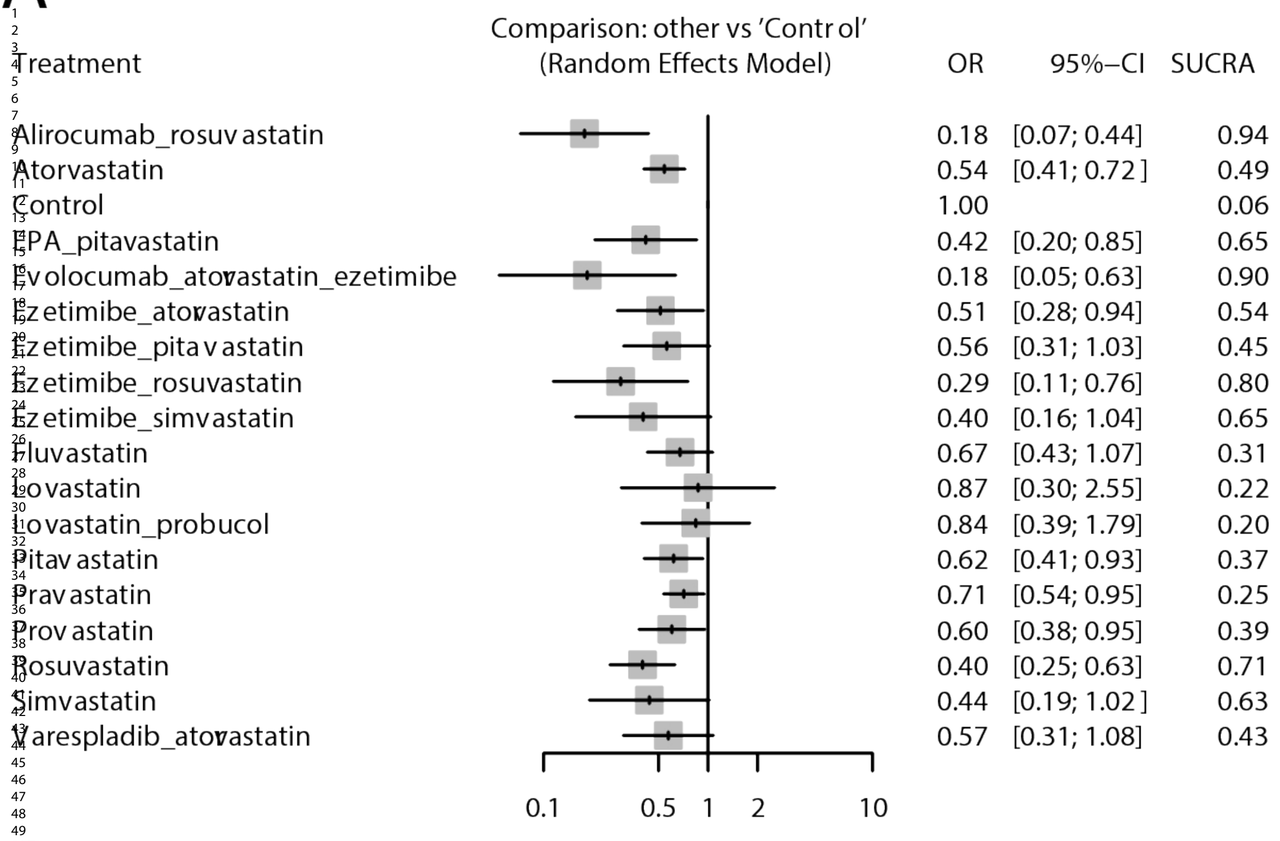

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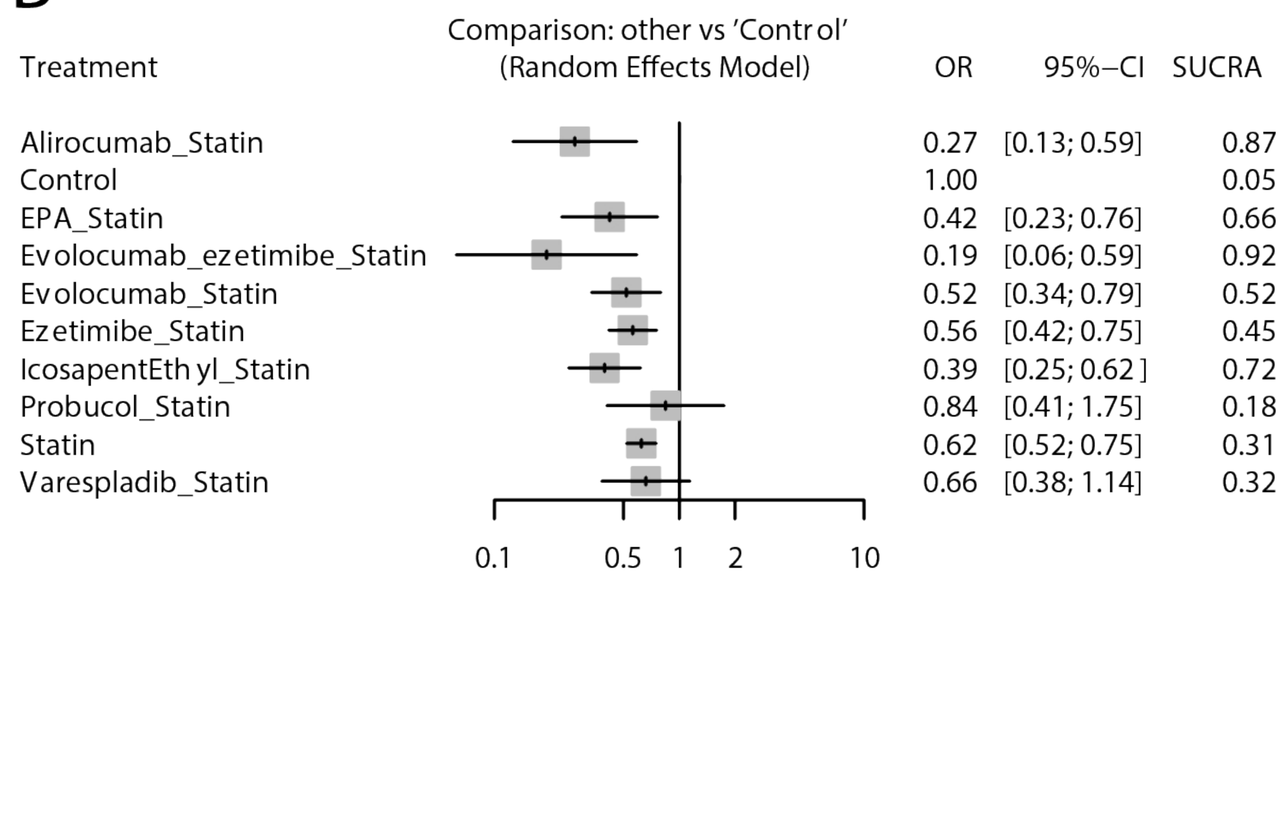

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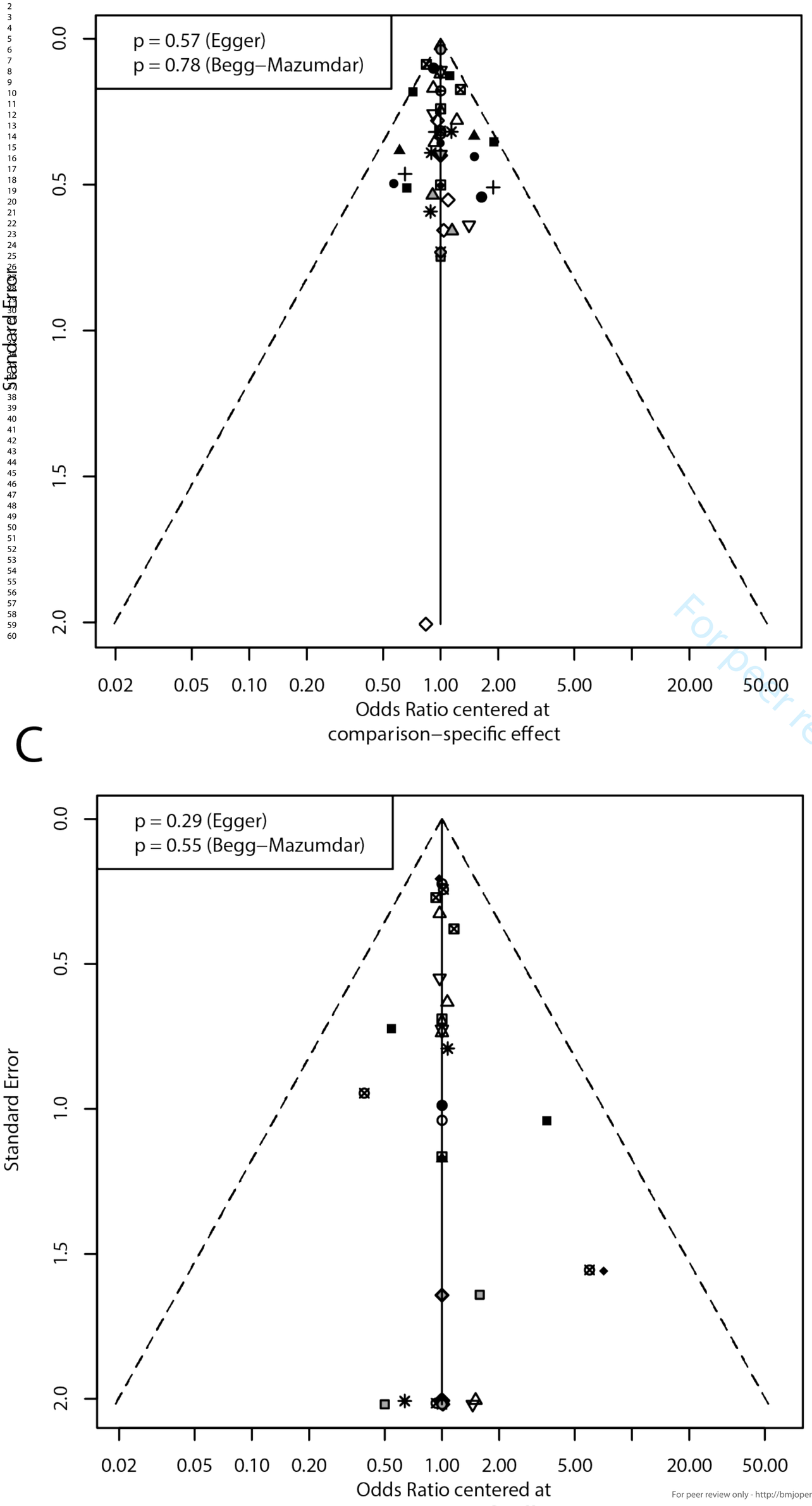

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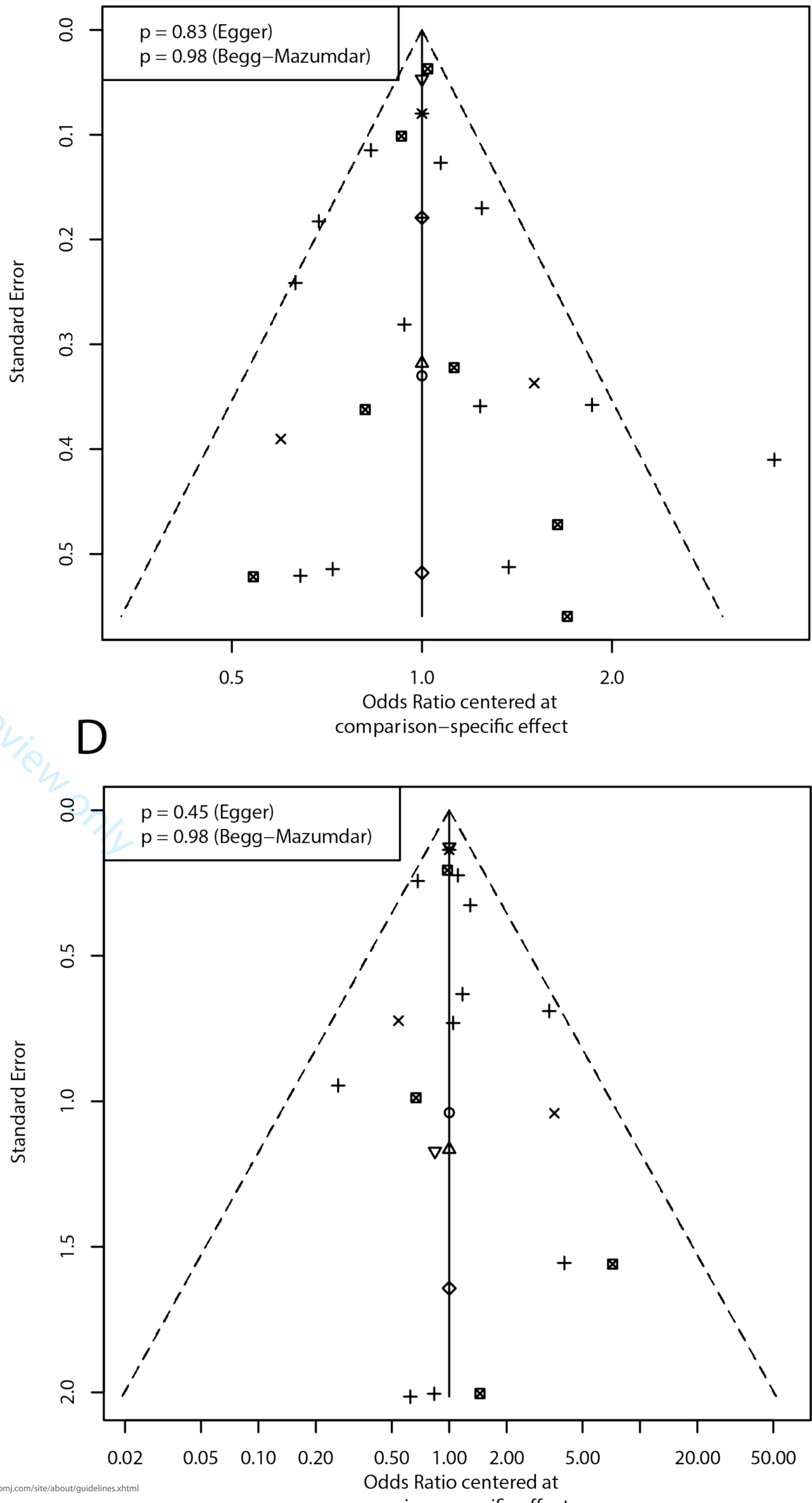

C

D

The full search strategy for all databases.

a. The search query used in PubMed database without language or other additional limits.

Search number	Query	Results
4	((#1) AND (#2)) AND (#3)	553
3	Random* or randomized or randomised	1,591,835
2	"percutaneous coronary intervention" OR "Coronary angioplasty"	61,003
1	Statin or Simvastatin or Rosuvastatin or Atorvastatin or Fluvastatin or Lovastatin or Pravastatin or Mevastatin or ezetimibe or "Icosapent Ethyl" or "Bempedoic acid" or fibrate or evolocumab or Alirocumab or evinacumab or Volanesorsen or Vupanorsen or Pelacarsen or Olezarsen or Pelacarsen or Inclisiran or olpasiran or Lipid-lowering	88,902

b. The search strategy used in EmBase database without language or other additional limits.

No.	Query	Results
#4	#1 AND #2 AND #3	1308
#3	random* OR randomized	2080906
#2	percutaneous coronary intervention' OR 'coronary angioplasty'	131280
#1	'statin'/exp OR statin OR 'simvastatin'/exp OR simvastatin OR 'rosuvastatin'/exp OR rosuvastatin OR 'atorvastatin'/exp OR atorvastatin OR 'fluvastatin'/exp OR fluvastatin OR 'lovastatin'/exp OR lovastatin OR 'pravastatin'/exp OR pravastatin OR 'pitavastatin'/exp OR pitavastatin OR 'mevastatin'/exp OR mevastatin OR 'ezetimibe'/exp OR ezetimibe OR 'eicosapentaenoic acid'/exp OR 'eicosapentaenoic acid' OR 'icosapent ethyl'/exp OR 'icosapent ethyl' OR 'bempedoic acid'/exp OR 'bempedoic acid' OR 'fibrate'/exp OR fibrate OR 'bezafibrate'/exp OR bezafibrate OR 'gemfibrozil'/exp OR gemfibrozil OR 'fenofibrate'/exp OR fenofibrate OR 'ciprofibrate'/exp OR ciprofibrate OR 'evolocumab'/exp OR evolocumab OR 'alirocumab'/exp OR alirocumab OR evinacumab OR 'volanesorsen'/exp OR volanesorsen OR 'vupanorsen'/exp OR vupanorsen OR 'pelacarsen'/exp OR pelacarsen OR 'olezarsen'/exp OR olezarsen OR 'inclisiran'/exp OR inclisiran OR 'olpasiran'/exp OR olpasiran OR 'lipid lowering'	167569

c. The search strategy used in Cochrane library database without language or other additional limits.

ID	Search	Hits

#1	(Statin OR Simvastatin OR Rosuvastatin OR Atorvastatin OR Fluvastatin OR Lovastatin OR Pravastatin OR Pitavastatin or Mevastatin OR ezetimibe OR "Eicosapentaenoic Acid" OR "Icosapent Ethyl" OR "Bempedoic acid" OR Fibrate OR Bezafibrate OR Gemfibrozil OR Fenofibrate OR Ciprofibrate OR Evolocumab OR Alirocumab OR Evinacumab OR Volanesorsen OR Vupanorsen OR Pelacarsen OR Olezarsen OR Inclisiran OR Olpasiran OR Lipid-lowering)	19395
#2	"Percutaneous coronary intervention" OR "Coronary angioplasty"	13623
#3	Random* OR randomized	1346916
#4	#1 AND #2 AND #3	690

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	***P.1***
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	P.2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	***P.3-P.4***
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	P.4
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	P.4- P.5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	***P.5-P.6***
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P.5
Search	8	Present full electronic search strategy for at least one	P.5

		database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P.5-P.6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P.6-P.7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P.6-P.7
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	***P.7***
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P.7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	P.7
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	P.7
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	P.7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**P.7**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	***n/a***

RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	P.8
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	***P.10-P.12***
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	***P.10-P.12***
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	P.9-P.10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	P.9-P.10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	***P.10-P.12***
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	***P.10-P.12***
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	***P.10-P.12***
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	P.10-P.12
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	***n/a***
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	P.12

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	P.15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P.16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	***P.16***

PICOS = population, intervention, comparators, outcomes, study design.