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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

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4 1 **Effectiveness of lipid-lowering therapy on mortality and**
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7 2 **major adverse cardiovascular event outcomes in patients**
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9 3 **undergoing percutaneous coronary intervention: a network**
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11 4 **meta-analysis of randomized controlled trials**

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35
36 14 **Abstract**

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39 15 **Objective**

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42 16 This study will assess the benefits of different lipid-lowering regimens on the risk of
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44 17 MACEs and mortality in the post-PCI population by network meta-analysis.

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47 18 **Methods**

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49 19 Public literature databases, including PubMed, Embase, and the Cochrane Library,
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51
52 20 were searched from inception to August 2022. Randomized controlled trials (RCTs)
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54 21 on lipid-lowering regimens in post-PCI populations were included and analyzed. The
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57 22 outcomes were the incidence of all-cause mortality and MACE, whether reported as
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23 dichotomous or hazard ratio (HR) statistics.

24 **Results**

25 Thirty-nine RCTs were included. For MACEs, alirocumab plus rosuvastatin (OR:
26 0.18; 95% CI: 0.07-0.44;), evolocumab plus ezetimibe and statins (OR: 0.19; 95%
27 CI:0.06-0.59), eicosapentaenoic acid (EPA) plus pitavastatin (HR: 0.67; 95% CI:
28 0.49-0.96), and icosapent ethyl plus statins (HR: 0.73; 95% CI: 0.62-0.86) had
29 significant advantages and relatively high rankings. For mortality, rosuvastatin (OR:
30 0.30; 95% CI: 0.11-0.84), ezetimibe plus statins (OR: 0.55; 95% CI: 0.43-0.89) and
31 icosapent ethyl plus statins (OR: 0.66; 95% CI: 0.45-0.96) had significant advantages
32 compared to the control.

33 **Conclusion**

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

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

41 **Introduction**

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

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4 46 intervention (PCI) can quickly restore myocardial perfusion^[3]. Although the
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7 47 development of technological and procedural PCI have resulted in substantial
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10 48 improvements in clinical outcomes, recurrent coronary events may still occur after
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12 49 PCI^[4].

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14 50 The view of "residual cardiovascular risk" was introduced because MACE still occurs
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17 51 in some patients who received PCI during follow-up. PCI can treat focal
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20 52 manifestations of systemic progressive disease, but the residual risk of acute coronary
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22 53 syndrome is largely related to the systemic proatherosclerotic effect of poorly
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25 54 controlled cardiovascular risk factors^[5]. Lowering lipid levels, especially LDL-C, can
26
27 55 halt the progression of coronary atherosclerosis and improve cardiovascular outcomes.
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30 56 Based on this view, it is believed that long-term optimal lipid-lowering therapy is
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32 57 effective in reducing long-term cardiovascular events after PCI. However, the view
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35 58 was still subject to challenges.

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40 60 Based on data from the "Korea Acute Myocardial Infarction Registry", the proponents
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43 61 concluded that patients treated with statins had significantly lower rates of MACE,
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46 62 all-cause death, and cardiac death during the 2-year follow-up period after PCI
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49 63 application^[6]. However, a study of postoperative follow-up of PCI patients enrolled in
50
51 64 the Melbourne Interventional Group registry concluded that statins have no significant
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54 65 benefit to MACEs after PCI^[6]. The controversy may be based on two reasons: on the
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57 66 one hand, is that the optimal lipid reduction target may not be achieved by using
58
59 67 single statins^[7, 8]. On the other hand, long-term high-dose application of statins
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4 68 increases the risk of intracerebral hemorrhage and other side effects [9, 10].
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9 70 There is a consensus on preloading high-dose statins to reduce MACEs in the
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11 71 perioperative period with PCI [11, 12]. However, there is still insufficient evidence for
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14 72 the continued application of lipid-lowering drugs to reduce the risk of long-term
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17 73 MACE and mortality. This study will assess the benefits of different lipid-lowering
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19 74 regimens on the risk of MACEs and mortality in the post-PCI population by network
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22 75 meta-analysis.
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27 **Methods**

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30 78 This study was performed in accordance with Preferred Reporting Items for
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32 79 Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
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35 **Patient and Public Involvement**

36
37 81 None
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43 **Search strategy**

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45 84 Public literature databases, including PubMed, Embase, and the Cochrane Library,
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48 85 were searched from inception to August 2022 without language restrictions using the
49
50
51 86 following search terms: (lipid-lowering or statin or simvastatin or rosuvastatin or
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53 87 atorvastatin or fluvastatin or lovastatin or pravastatin or pitavastatin or mevastatin or
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56 88 ezetimibe or “eicosapentaenoic acid” or “icosapent ethyl” or “bempedoic acid” or
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58 89 fibrate or bezafibrate or gemfibrozil or fenofibrate or ciprofibrate or evolocumab or
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4 90 alirocumab or evinocumab or volanesorsen or vupanorsen or pelacarsen or olezarsen
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7 91 or inclisiran or olpasiran) and (“percutaneous coronary intervention” or “coronary
8
9 92 angioplasty”) and (random* or randomized or randomized). The references of
10
11
12 93 relevant systematic reviews and meta-analyses were also searched to avoid omissions.
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14 94 The two authors conducted literature retrieval independently, and any conflicts were
15
16
17 95 resolved through discussion with the third author.
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21 22 97 **Inclusion and exclusion criteria**

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24 98 The literature was included if it met the following criteria: 1, the study adopted a
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26
27 99 randomized controlled study design; 2, the study included patients who received PCI
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30 100 surgery or reported the subgroup of the population that received PCI; 3, the lipid-
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33 101 lowering regimen was applied to the population of the intervention group; 4, the
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35 102 control group used a different lipid-lowering agent or regimen; and 5, the study
36
37
38 103 reported the outcome of mortality and/or MACE. Exclusion criteria: 1, as preloading
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41 104 of statins before PCI had clear benefits, to determine whether application of lipid-
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43
44 105 lowering drugs after PCI also had beneficial effects. This work excluded the study on
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46
47 106 the preloading application of lipid-lowering drugs before PCI; 2, although high-dose
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50 107 lipid-lowering agents, such as statins, have a better lipid-lowering effect, long-term
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53 108 application may bring potential side effects [9, 13]. In this study, all agents were
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56 109 considered to be applied with reasonable doses, and dose–response studies were
57
58
59 110 excluded. In addition, repeatedly published studies, protocols, conference abstracts,
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111 111 reviews, comments and editorials were also excluded.

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6 113 Data extraction and quality assessment

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9 114 Two authors independently extracted the information from the included studies. The

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11 115 contents include the name of the first author, publication year, study location, sample

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14 116 size (population received PCI), study abbreviation and registration number, lipid-

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17 117 lowering intervention and control, and follow-up time.

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22 119 The outcomes analyzed were the incidence of all-cause mortality and MACE, whether

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24 120 reported as dichotomous or hazard ratio (HR) statistics based on Cox regression. The

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27 121 MACE outcome was selected to most closely approximate the composite endpoint,

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29 122 including mortality, MI, stroke, coronary revascularization, and restenosis. Study

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32 123 quality was assessed by two investigators using the Cochrane risk of bias assessment

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35 124 tool, which included random sequence generation, allocation concealment, blinding of

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38 125 participants and personnel, blinding of outcome assessment, incomplete outcome data,

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41 126 selective reporting, and other potential biases.

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46 128 Statistical analysis

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48 129 For each direct paired comparison, we used the odds ratios and their 95% confidence

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51 130 intervals (CIs) for dichotomous outcomes. The hazard ratios and their 95% CIs based

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54 131 on Cox regression results were also pooled for reporting. We conducted frequentist

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56 132 network meta-analysis (NMA) using random effect models with restricted maximum

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59 133 likelihood estimation to quantify network heterogeneity. The Q statistic was used to

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4 134 assess the sum of statistics for heterogeneity (within designs) and for overall
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6 135 inconsistency (between designs)^[14]. The ranking probabilities of each regimen were
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9 136 estimated using the surface under the cumulative ranking curve (SUCRA), and a
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11 137 comparison-adjusted funnel plot was used to examine potential publication biases in
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13
14 138 NMA. P values of less than 0.05 were considered to be statistically significant. The
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17 139 NMA was performed using R language with the “netmeta” package.
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21 22 141 **Results**

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24 142 After removing duplications, we obtained 1588 literature items. After a screen of the
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27 143 titles and abstracts, 1515 irrelevant studies were excluded. Seventy-three articles were
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30 144 screened for full text. The following articles were excluded: dose–response studies (8),
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32 145 no PCI population or subgroup was reported (6); no mortality or MACE-related
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35 146 outcomes were reported (6); repeated publication (5); study related to preloading of
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37
38 147 lipid-lowering agents (4); study not related to lipid-lowering agents (3); protocol (1);
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40 148 non-RCT design (1). Finally, 39 articles were included containing 54478 patients after
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43 149 PCI^[15-53] (Figure 1).
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48 151 Among the included studies, the publication period ranged from 1991 to 2022. The
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51 152 research locations were mainly in Asia (China, Japan and South Korea), Europe
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54 153 (Netherlands, France, and Italy), America, and multiple centers. There were 10 studies
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56 154 with sample sizes greater than 1000 patients. There were also 22 studies with publicly
57
58
59 155 available clinical study registration numbers (Table 1). In terms of design quality, all
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156 included studies were RCTs. Therefore, the design quality is generally high. The main
 157 factors potentially affecting design quality were the blinding of participants and
 158 personnel and blinding of outcome assessment (Figure 2). However, as the desired
 159 outcomes were mortality and MACE, the subjective factors of the investigator had
 160 little influence on the outcomes.

161 **Table 1. The characteristics of included studies**

Study	Location	Sample size	Abbreviation	Register ID	Intervention	Control	Follow-up#
Lorenz Råber 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	Pravastatin	2Y
Han Yaling 2009 [41]	China	1275	-	NCT00405717	Atorvastatin	Pravastatin	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]	Netherlands	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

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163 Abbreviations: EPA: eicosapentaenoic acid.

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

165 As two studies did not specify the types of statins, the network meta-analysis will be

166 divided into two parts. One part was analyzed based on specific types of statins, and

167 the other was based on taking statins as a whole. For the dichotomous results of

168 MACE, the NMA based on specific types of statins included 18 lipid-lowering

169 regimens. The Q test for heterogeneity was $p = 0.07$, and for inconsistency, it was $p =$

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4 170 0.16, indicating no evidence for heterogeneity and inconsistency in the NMA.
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7 171 In pairwise comparisons with the control, alirocumab plus rosuvastatin (OR: 0.18; 95%
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9 172 CI: 0.07-0.44; SUCRA: 0.94), evolocumab plus atorvastatin and ezetimibe (OR: 0.18;
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11 173 95% CI: 0.05-0.63; SUCRA: 0.90), ezetimibe plus rosuvastatin (OR: 0.29; 95% CI:
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13 174 0.11-0.76; SUCRA: 0.80) have significant advantages and relatively high SUCRA
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15 175 rankings. No potential publication bias was found according to the comparison-
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17 176 adjusted funnel plot (Figure 3).
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25 178 In the NMA based on taking statins as a whole, ten regimens were analyzed.
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27 179 Evolocumab plus ezetimibe and statins (OR: 0.19; 95% CI: 0.06-0.59; SUCRA: 0.92),
28
29 180 alirocumab plus statins (OR: 0.27; 95% CI: 0.13-0.59; SUCRA: 0.87), and coscapent
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31 181 ethyl plus statins (OR: 0.39; 95% CI: 0.25-0.62; SUCRA: 0.72) have significant
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33 182 advantages and relatively high SUCRA rankings. No potential publication bias was
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35 183 found.
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43 185 For the HR results of MACEs, the NMA based on specific types of statins included
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45 186 nine regimens. The Q test for heterogeneity was $p = 0.964$ and because the network
46
47 187 comparisons lack loops. Therefore, the results were considered consistent. Compared
48
49 188 to the control, eicosapentaenoic acid (EPA) plus pitavastatin (HR: 0.67; 95% CI:
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51 189 0.49-0.96; SUCRA: 0.91), atorvastatin (HR: 0.76; 95% CI: 0.63-0.90; SUCRA: 0.83),
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53 190 and varespladib plus atorvastatin (HR: 0.77; 95% CI: 0.61-0.97; SUCRA: 0.77) have
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55 191 significant advantages and relatively high SUCRA rankings. Potential publication bias
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4 192 was not analyzed due to a smaller number of included studies.
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9 194 In the NMA based on taking statins as a whole, seven regimens were analyzed. EPA
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11 195 plus statins (HR: 0.60; 95% CI: 0.42-0.85; SUCRA: 0.96) and icosapent ethyl plus
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13 196 statins (HR: 0.73; 95% CI: 0.62-0.86; SUCRA: 0.81) had significant advantages over
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17 197 the control.
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22 199 For the dichotomous results of mortality, the NMA based on specific types of statins
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24 200 included 17 lipid-lowering regimens. The Q test for heterogeneity was $p = 0.78$, and
25
26 201 for inconsistency, it was $p = 0.99$. Due to the rare occurrence of events, the results of
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28
29 202 the comparison were low precision with a large standard error. Compared to the
30
31 203 control, only rosuvastatin (OR: 0.30; 95% CI: 0.11-0.84; SUCRA: 0.79) showed a
32
33 204 significantly better effect. Ezetimibe plus rosuvastatin had a relatively high SUCRA
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35 205 ranking, but there was no significant difference compared to the control (OR: 0.14; 95%
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37 206 CI: 0.02-1.26; SUCRA: 0.86). No potential publication bias was found (Figure 4).
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45 208 In the NMA based on taking statins as a whole, nine regimens were analyzed.
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47 209 Ezetimibe plus statins (OR: 0.55; 95% CI: 0.43-0.89; SUCRA: 0.75) and icosapent
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49 210 ethyl plus statins (OR: 0.66; 95% CI: 0.45-0.96; SUCRA: 0.63) had significant
50
51 211 advantages compared with the blank control group. No potential publication bias
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53 212 existed. NMA analysis was not performed due to the small number of studies
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56 213 reporting HR for mortality (Figure 5).
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6 215 **Discussion**

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9 216 This study analyzed the benefits of lipid-lowering therapy on mortality and MACE
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11 217 outcomes in patients who received PCI by network meta-analysis. The results showed
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14 218 that several lipid-lowering regimens could reduce the risk of MACEs compared with
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17 219 the blank control. Icosapent ethyl plus statins had the benefit of reducing both the risk
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19 220 of MACEs and mortality. However, EPA plus statins had more advantages in
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22 221 reducing the risk of MACEs. Of note, based on the current evidence, alirocumab and
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25 222 evolocumab plus statins had obvious advantages in reducing the risk of MACEs but
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27 223 had no obvious benefit in reducing the risk of mortality.

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32 225 EPA is a long-chain omega-3 polyunsaturated fatty acid. Long-term intake of EPA
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35 226 can reduce the residual cardiovascular risk to reduce the risk of MACEs^[54]. In terms
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38 227 of pathological mechanisms, EPA combined with pitavastatin can reduce the lipid
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41 228 volume of coronary artery plaque and total atherosclerotic plaque volume in patients
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43 229 who receive PCI, which may be the reason for the reduced risk of MACEs ^[55].

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48 231 Icosapent ethyl is a highly purified and stable eicosapentaenoic acid ethyl ester that
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51 232 has potential higher anti-inflammatory, antioxidant, plaque stability and cell
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53 233 membrane stability effects ^[56]. In the NMA results, icosapent ethyl plus statins had
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56 234 significant benefits for either mortality or MACEs in patients who received PCI,
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59 235 which was an ideal regimen for the population.

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6 237 Ezetimibe inhibits the absorption of cholesterol and has a synergistic lipid-lowering
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9 238 pharmacological effect with statins to further reduce the risk of death and MACE. In
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11 239 particular, when combined with rosuvastatin, it has a stronger lipid-lowering effect
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14 240 with a high safety profile without the risk of drug interactions^[57]. Our NMA results
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17 241 also showed that it can reduce the risk of MACE and mortality. According to the
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19 242 guidelines for the management of dyslipidemia from the European Society of
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22 243 Cardiology and the European Atherosclerosis Society, ezetimibe was recommended if
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24 244 the LDL-C level was not reached^[58, 59]. The American College of Cardiology
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27 245 guidelines also recommend adding ezetimibe when using maximally tolerated statin
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30 246 therapy and if LDL-C levels remain ≥ 70 mg/dL^[60]. These benefits have also been
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33 247 demonstrated in the secondary prevention of PCI.

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38 249 Alirocumab and evolumab are both proprotein convertase subtilisin/kexin type 9
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40 250 inhibitors (PCSK9i), which can increase the level of LDL receptor in the liver, thus
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43 251 improving the ability of the liver to bind LDL-C and reducing the level of peripheral
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45 252 LDL-C^[61]. There was also a synergistic lipid-lowering pharmacological effect when
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48 253 PCSK9i was combined with statins that significantly reduced LDL-C and
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51 254 atherosclerosis event risk; however, there was still controversy regarding the mortality
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53 255 risk reduction^[62]. It has been suggested that the powerful effect of PCSK9I on
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56 256 reducing LDL-C predisposes patients to hypocholesterolemia, which will increase the
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59 257 risk of cerebral hemorrhage^[63, 64]. On the other hand, PCSK9i could not reduce serum
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4 258 inflammatory factors, suggesting that it may not reduce the risk of residual
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6 259 inflammation in the post-PCI population [65].
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11 261 In the results of this study, lipid-lowering therapy strategies had general advantages in
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14 262 reducing MACE risk. However, for all-cause mortality, the advantage of lipid-
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17 263 lowering therapy was not obvious. Based on dichotomous outcomes of mortality,
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20 264 some strategies may even have a tendency to increase the mortality risk. This
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22 265 challenges the opinion that lipid-lowering therapy is recommended after PCI [66]. A
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25 266 large sample size retrospective study suggests that statins can reduce the risk of all-
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27 267 cause death in patients with coronary artery disease undergoing PCI, regardless of
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30 268 personal cholesterol levels [67]. Alternatively, the “Lipid Paradox” view has been
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33 269 proposed and indicated that higher levels of LDL-C and triglycerides on admission
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36 270 are associated with better clinical outcomes. Especially in patients with ST-elevation
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38 271 myocardial infarction, lower LDL-C levels were associated with worse mortality
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40 272 outcomes [68]. However, this view is also controversial [69].
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45 274 On the other hand, it is possible that the contribution of LDL-C reduction to the risk
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48 275 of mortality outcomes is obscured by the other confounding factors. For example,
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51 276 inflammatory status may also have an important impact on patient mortality risk. In a
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54 277 cohort of post-PCI patients with low LDL-C levels, residual inflammatory risk also
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56 278 had a significant effect on overall mortality [70]. C-reactive protein can also predict
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59 279 long-term mortality in post-PCI patients independent of LDL-C levels [71]. In addition,
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4 280 cardiac remodeling also has an important impact on the survival outcome of people
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6 281 after PCI [72].
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11 283 In conclusion, the results of this study suggest that EPA, especially icosapent ethyl,
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14 284 plus statins had a beneficial effect on reducing the risk of MACEs and mortality in
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17 285 post-PCI patients. PCSK9i plus statins was able to reduce the risk of MACEs, but the
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20 286 risk of mortality remained unclear.
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24 288 There are still several limitations in this study. First, this study was based on the study
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27 289 level instead of the individual level, making it difficult to consider the individual
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30 290 confounding factors in the analysis. Second, two included studies did not specify the
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33 291 type of statins, so our study had to be analyzed separately according to whether all
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36 292 statins were considered as a whole. Third, the criteria for defining MACEs varied
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39 293 among studies that contributed to heterogeneity among the study results. Fourth,
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42 294 many included studies reported only dichotomous outcomes but did not report the HR
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45 295 results, resulting in the incompleteness of the relevant analysis results.
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47 296

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51 300 **Author contributions**

52 301 Chang-Jiang Deng completed the manuscript, Ju Yan, Ting-Ting Wu and Ying Pan
53
54
55 302 guided the data analysis and the production of the figures, All the authors read and
56
57
58 303 approved the final manuscript.
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9
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11 309 the datasets used or analysed during the current study are available from the
12
13 310 corresponding author on reasonable request.

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15 311

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17 312 **Declarations**

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20 314 **Ethics approval and consent to participate**

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22 315 This study does not involve human participants and ethical approval was not required.

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26 317 **Consent for publication**

27 318 not applicable.

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31 320 **Competing interests**

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33 321 The authors declare that they have no competing interests.

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35 322 **References**

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11 621 **Figure 1.** Flowchart of the study selection process for eligible studies

14 622 **Figure 2.** Methodological quality assessment of included studies

17 623 **Figure 3.** Network plots of comparisons for major outcomes included in the analyses.

19 624 A: dichotomous results of MACE based on specific types of statins; B: dichotomous
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22 625 results of MACE based on taking statins as a whole; C: hazard ratio results of MACE
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24 626 based on specific types of statins; D: hazard ratio results of MACE based on taking
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26 627 statins as a whole; E: dichotomous results of mortality based on specific types of
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28 628 statins; F: dichotomous results of mortality based on taking statins as a whole.

32 629 **Figure 4.** Forest plots of lipid-lowering therapy compare to control for outcomes in
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35 630 network meta-analysis with SUCRA ranking results. A: dichotomous results of
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37 631 MACE based on specific types of statins; B: dichotomous results of MACE based on
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39 632 taking statins as a whole; C: hazard ratio results of MACE based on specific types of
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41 633 statins; D: hazard ratio results of MACE based on taking statins as a whole; E:
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43 634 dichotomous results of mortality based on specific types of statins; F: dichotomous
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45 635 results of mortality based on taking statins as a whole.

50 636 **Figure 5.** The comparison-adjusted funnel plot for assessing all main outcomes. A:
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53 637 dichotomous results of MACE based on specific types of statins; B: dichotomous
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55 638 results of MACE based on taking statins as a whole; C: dichotomous results of
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57 639 mortality based on specific types of statins; D: dichotomous results of mortality based
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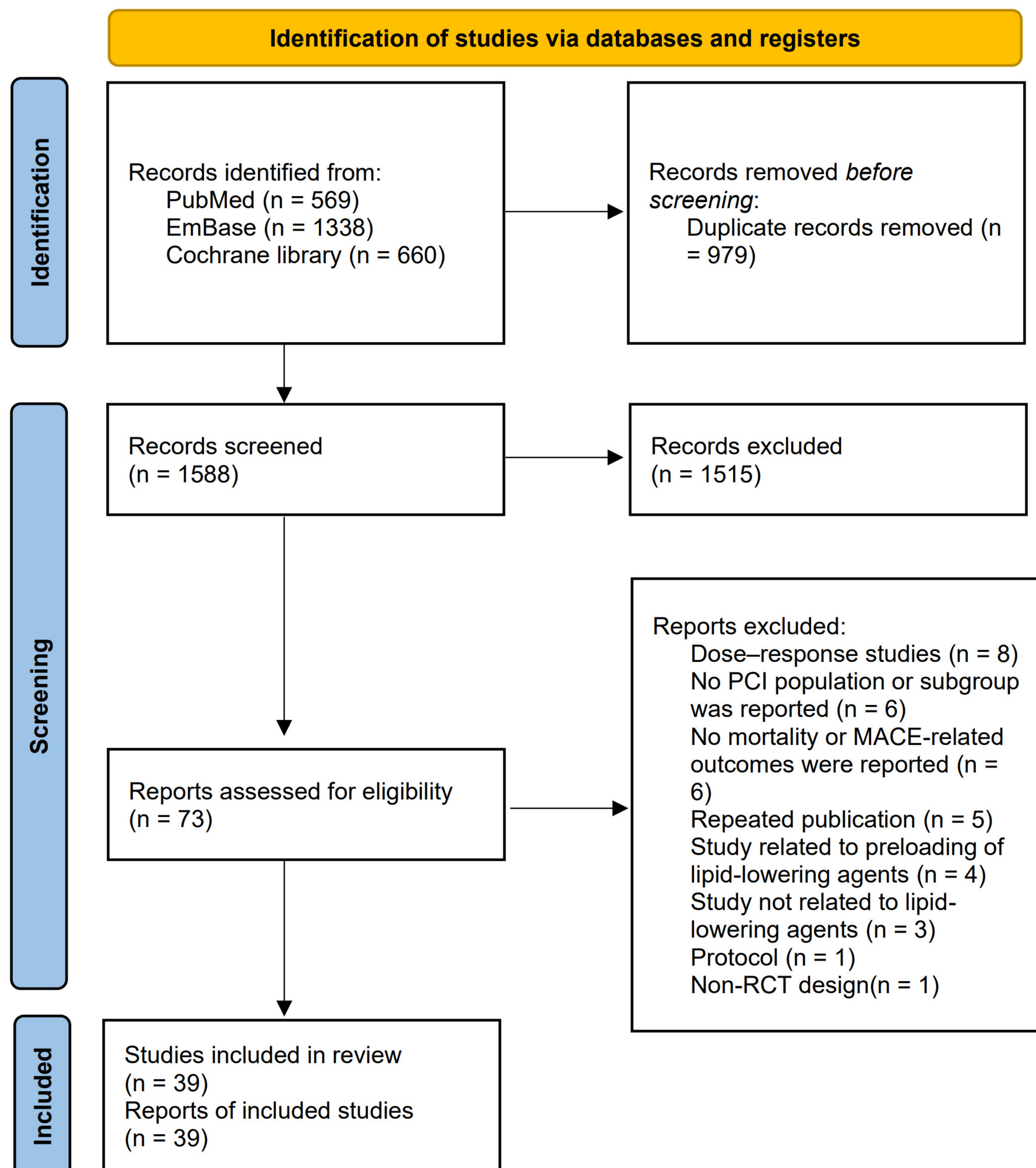
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PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



*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).

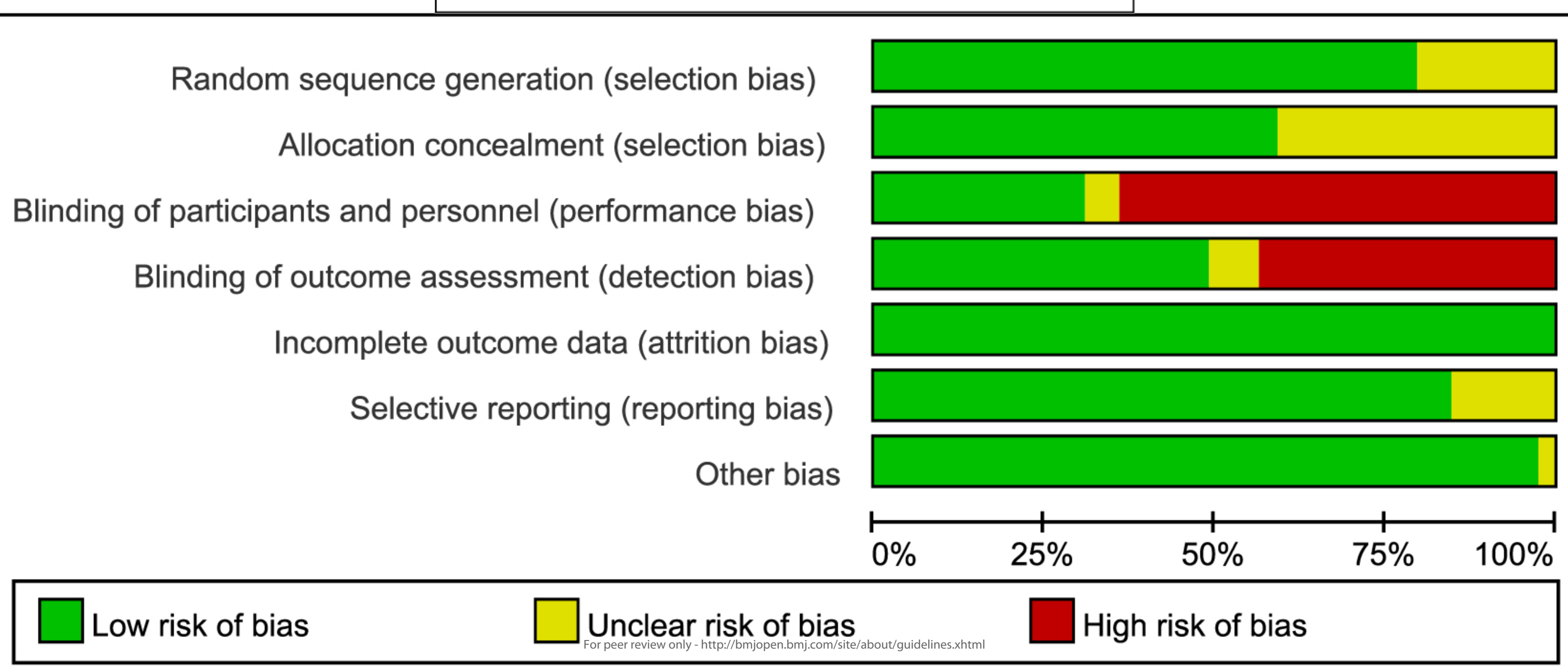
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

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

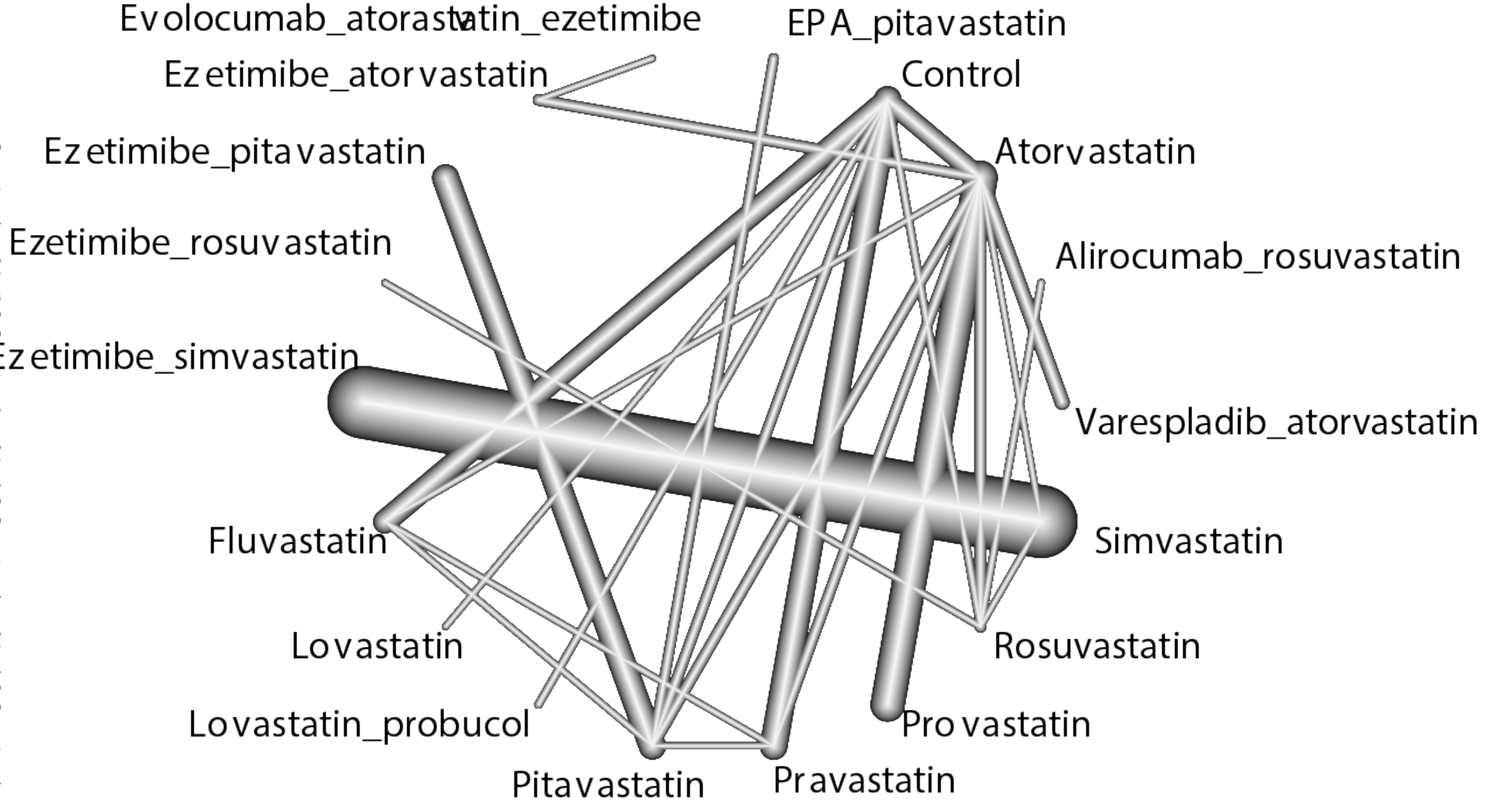
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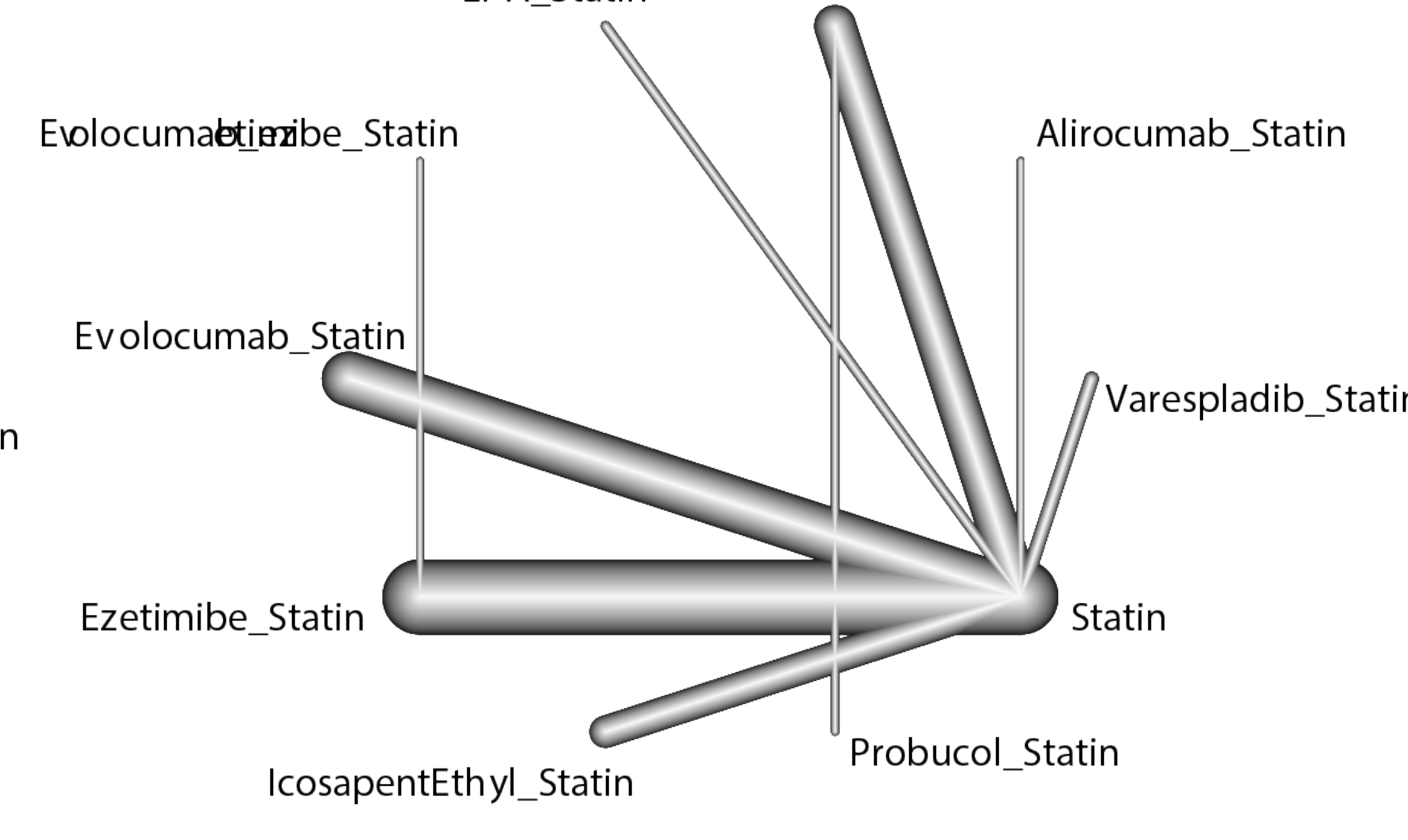
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Bae JH 2004	?	?	-	-	+	?	+
C. Michael Gibson 2009	+	+	+	+	+	+	+
Christopher P Cannon 2015	+	+	+	+	+	+	+
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Greg C. Flaker 1999	+	+	+	+	+	+	+
Hagiwara N 2017	+	?	-	+	+	+	+
Han J.G.H. Mulder 2000	+	+	+	+	+	+	+
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Haruhiko Onaka 1994	?	?	-	-	+	+	+
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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	+	?	-	-	+	+	?



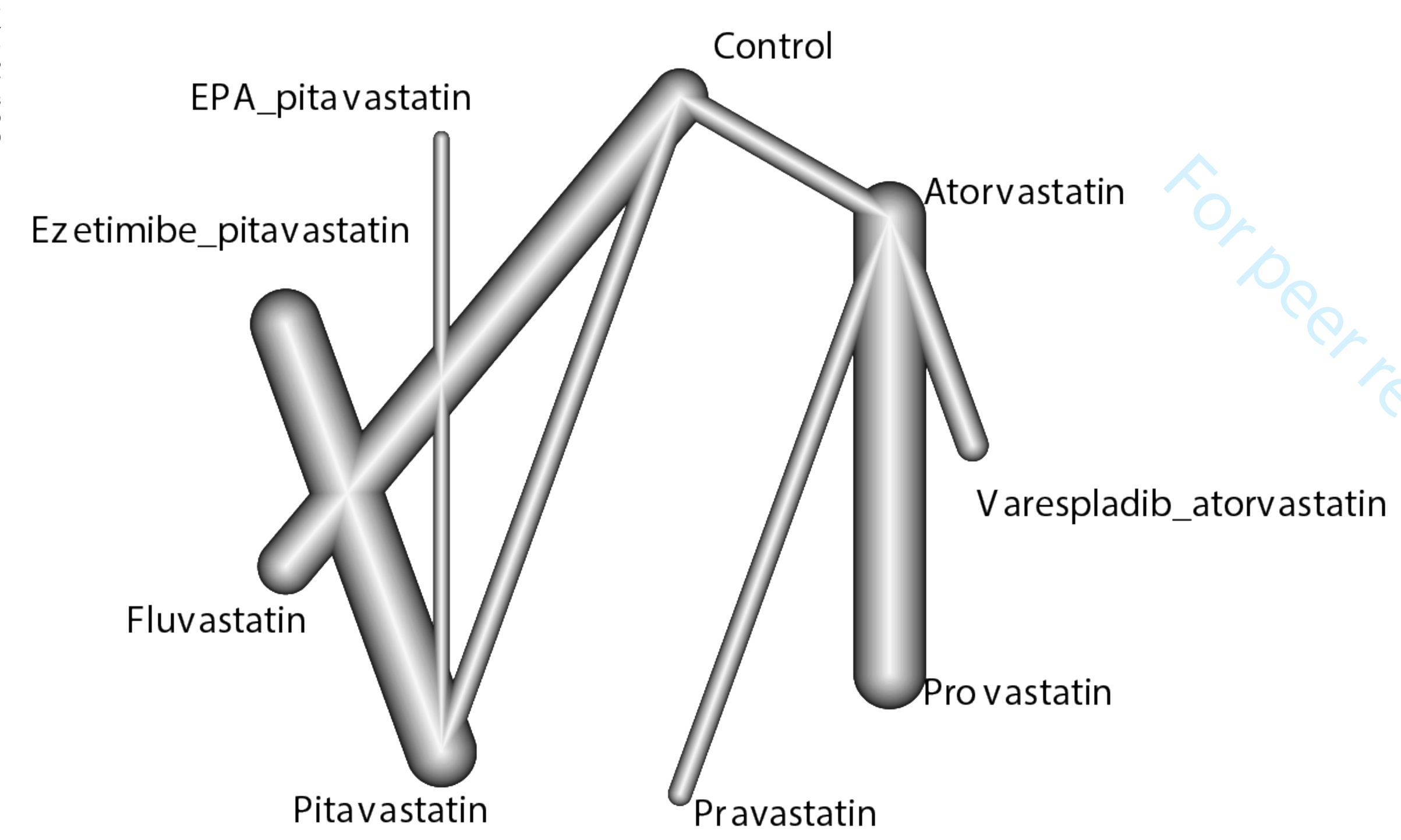
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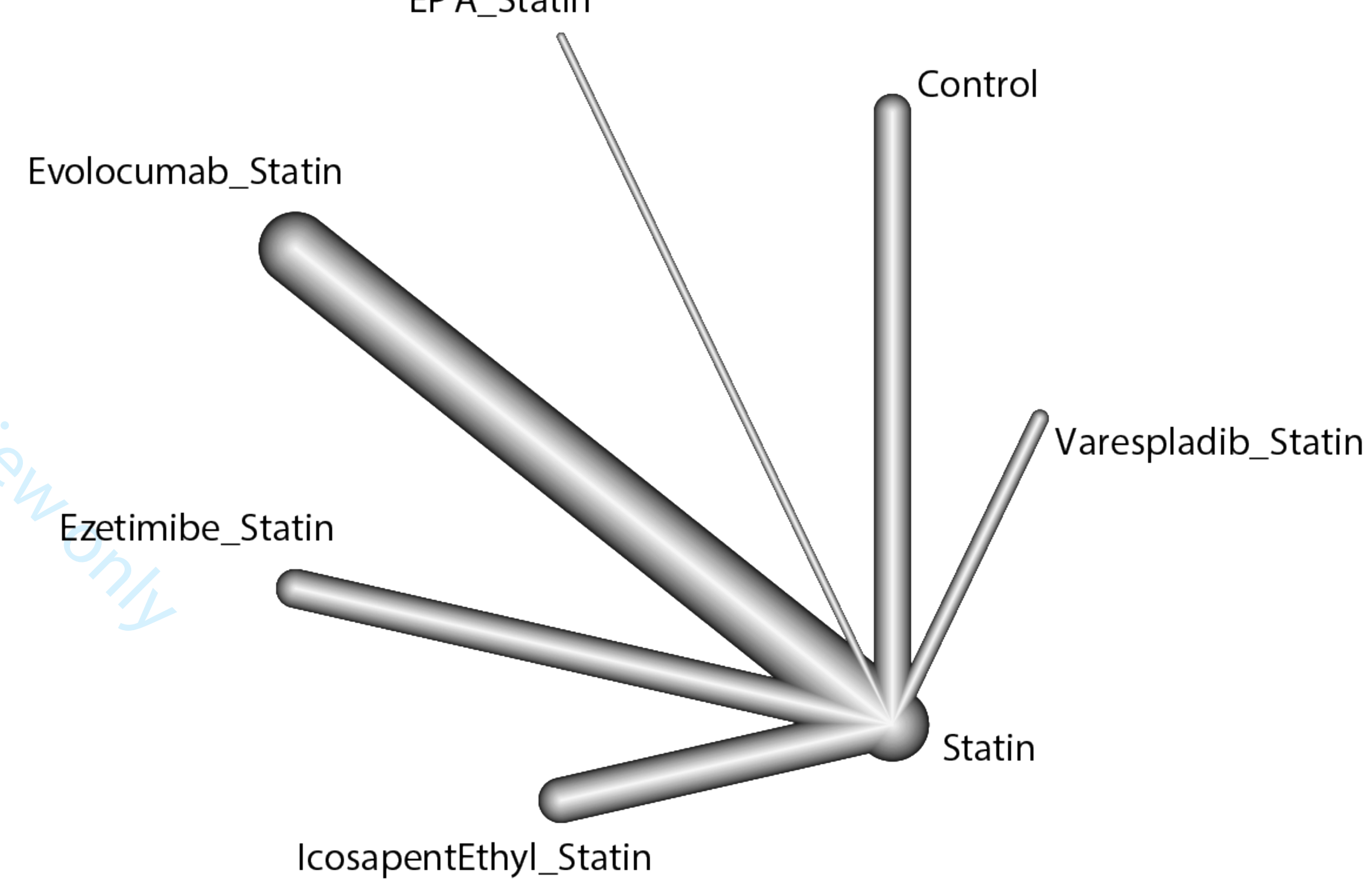
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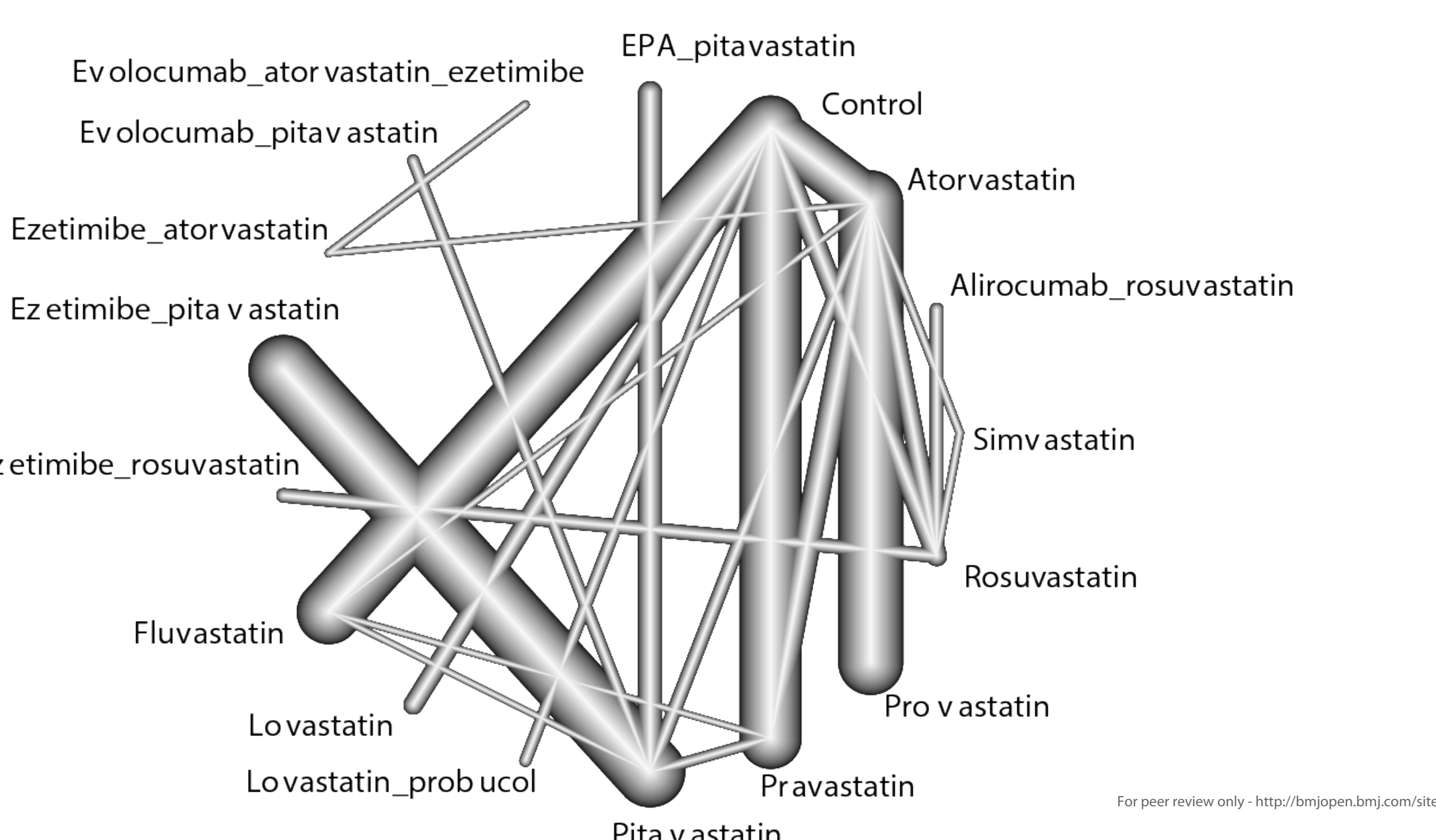
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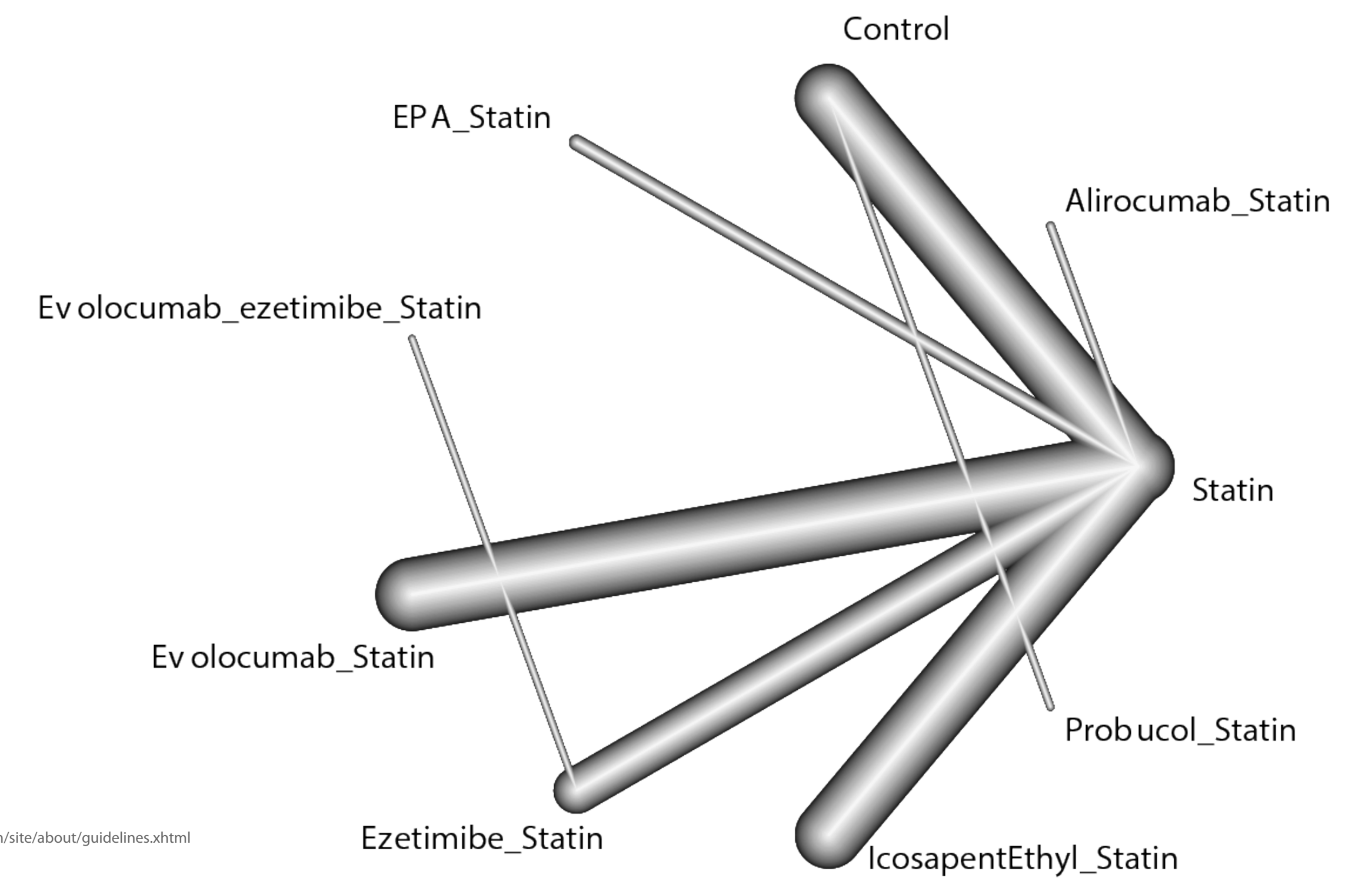
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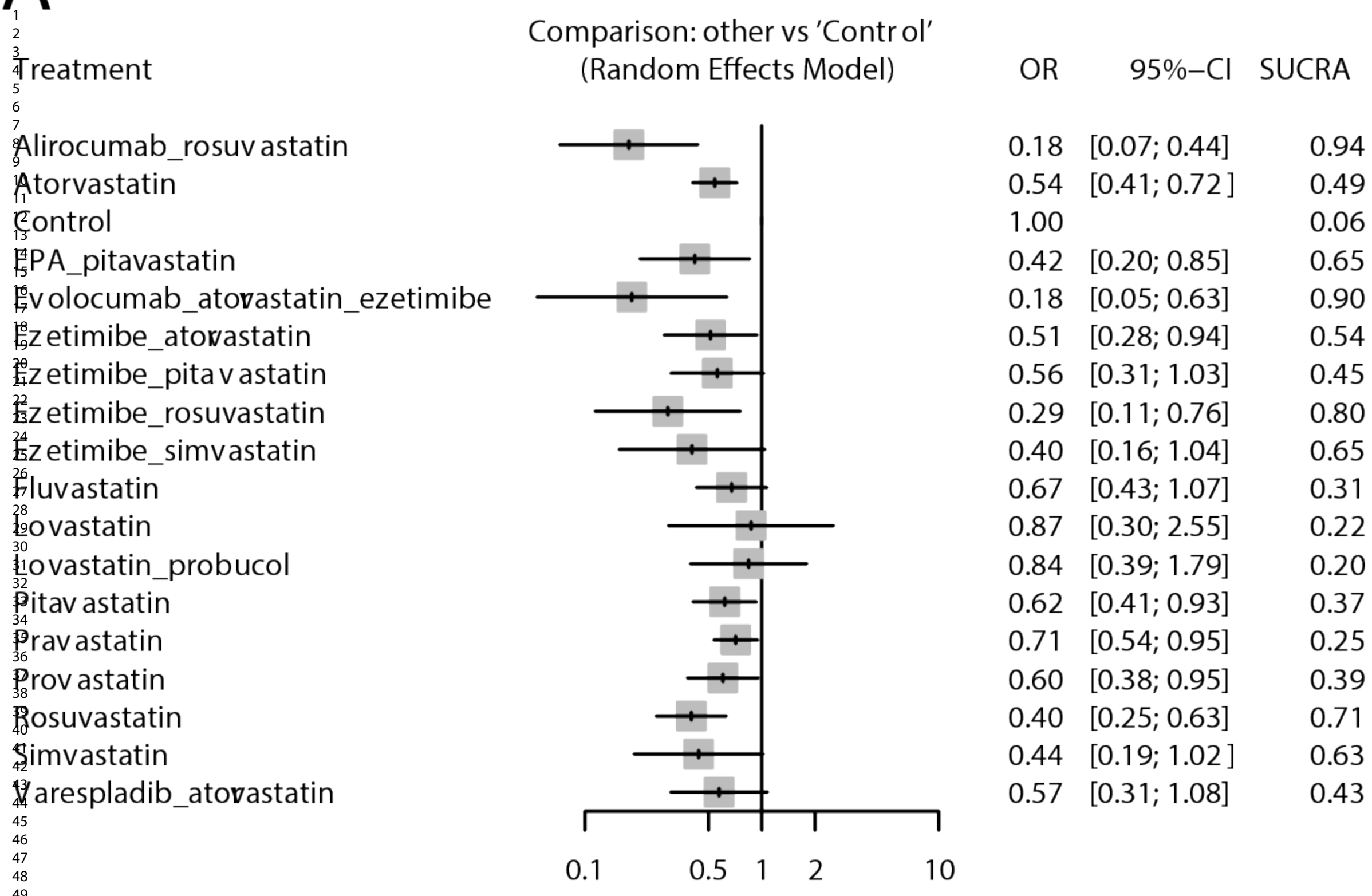


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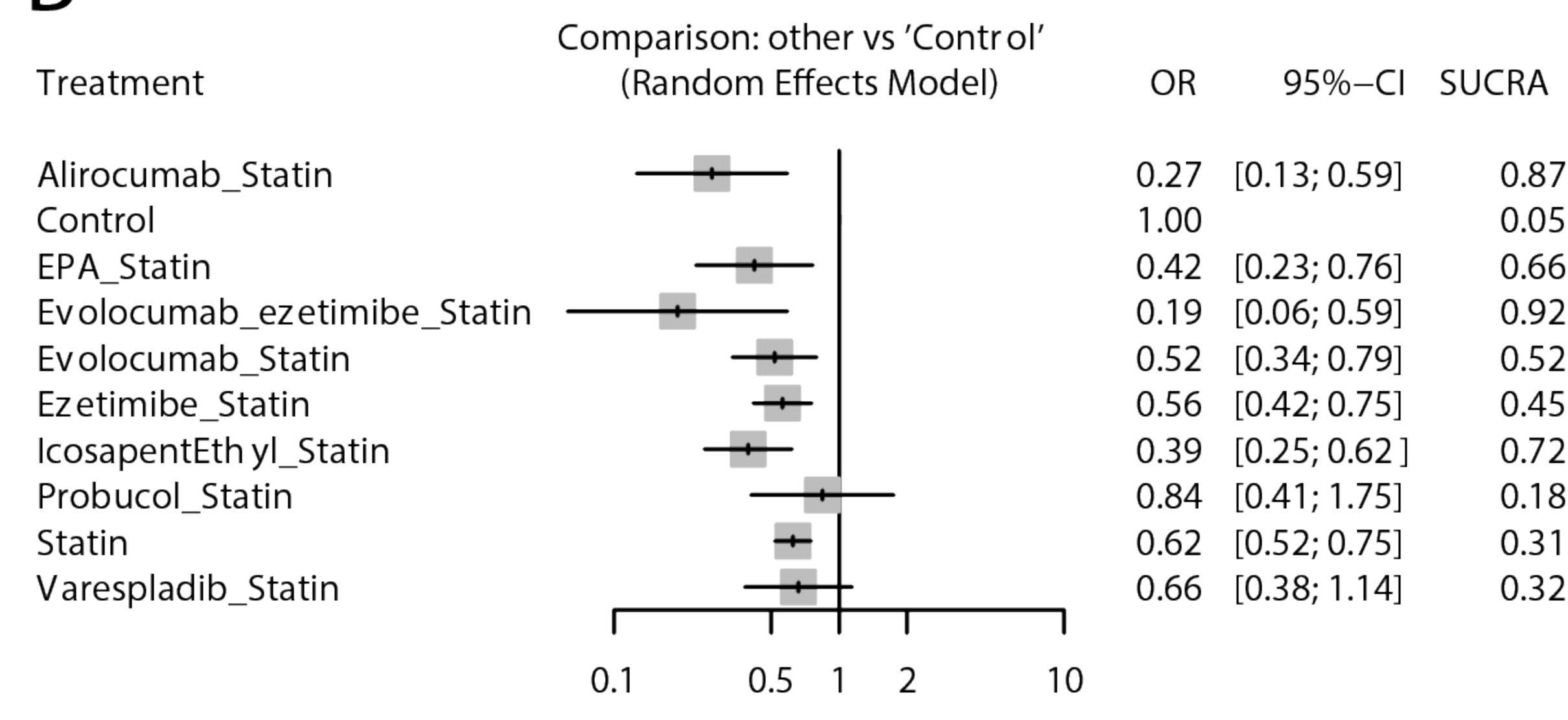


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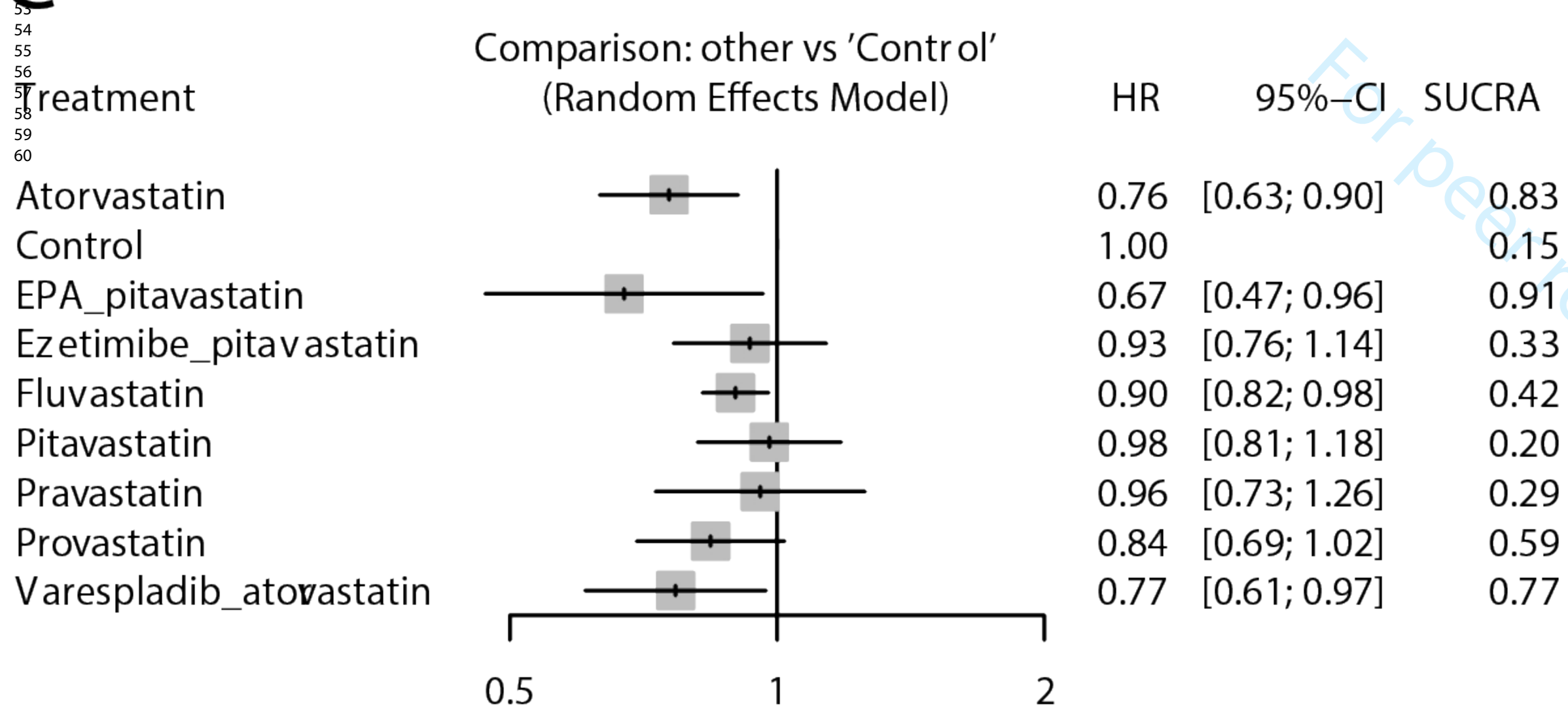
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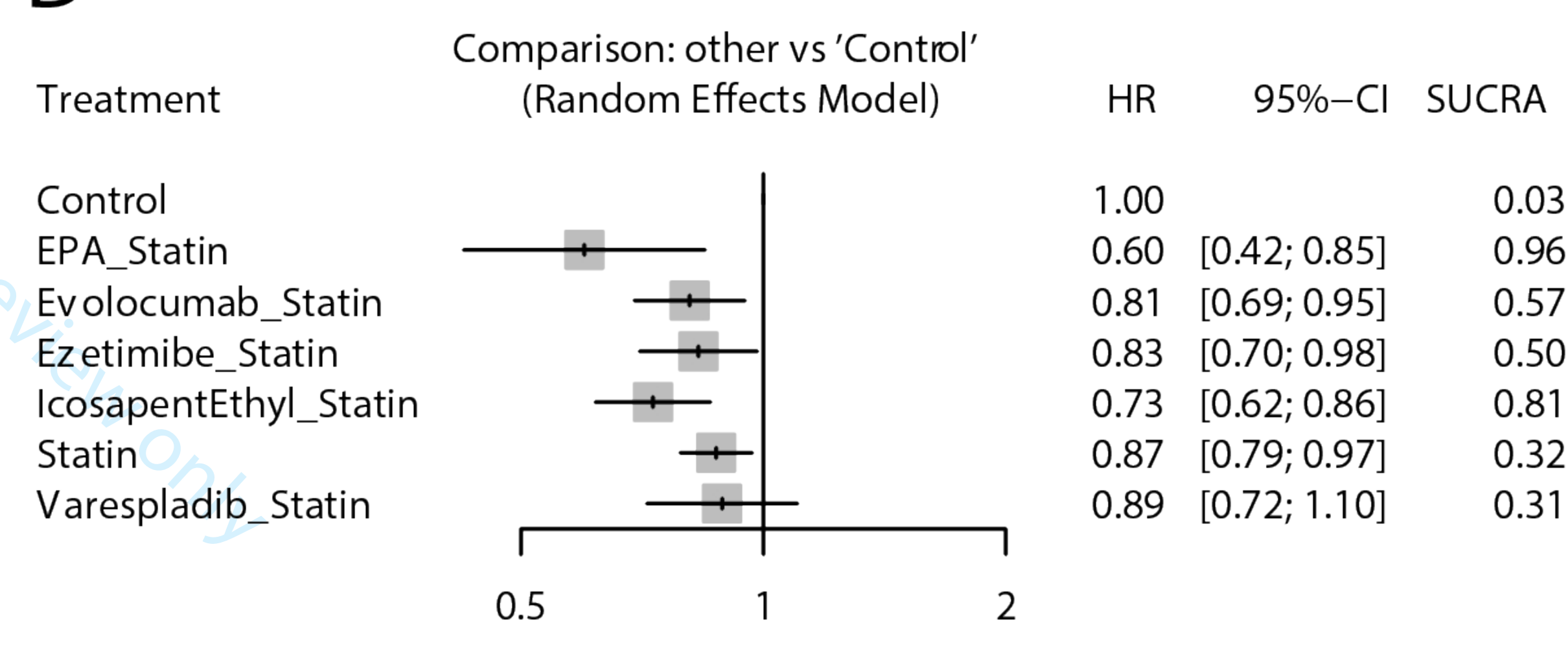
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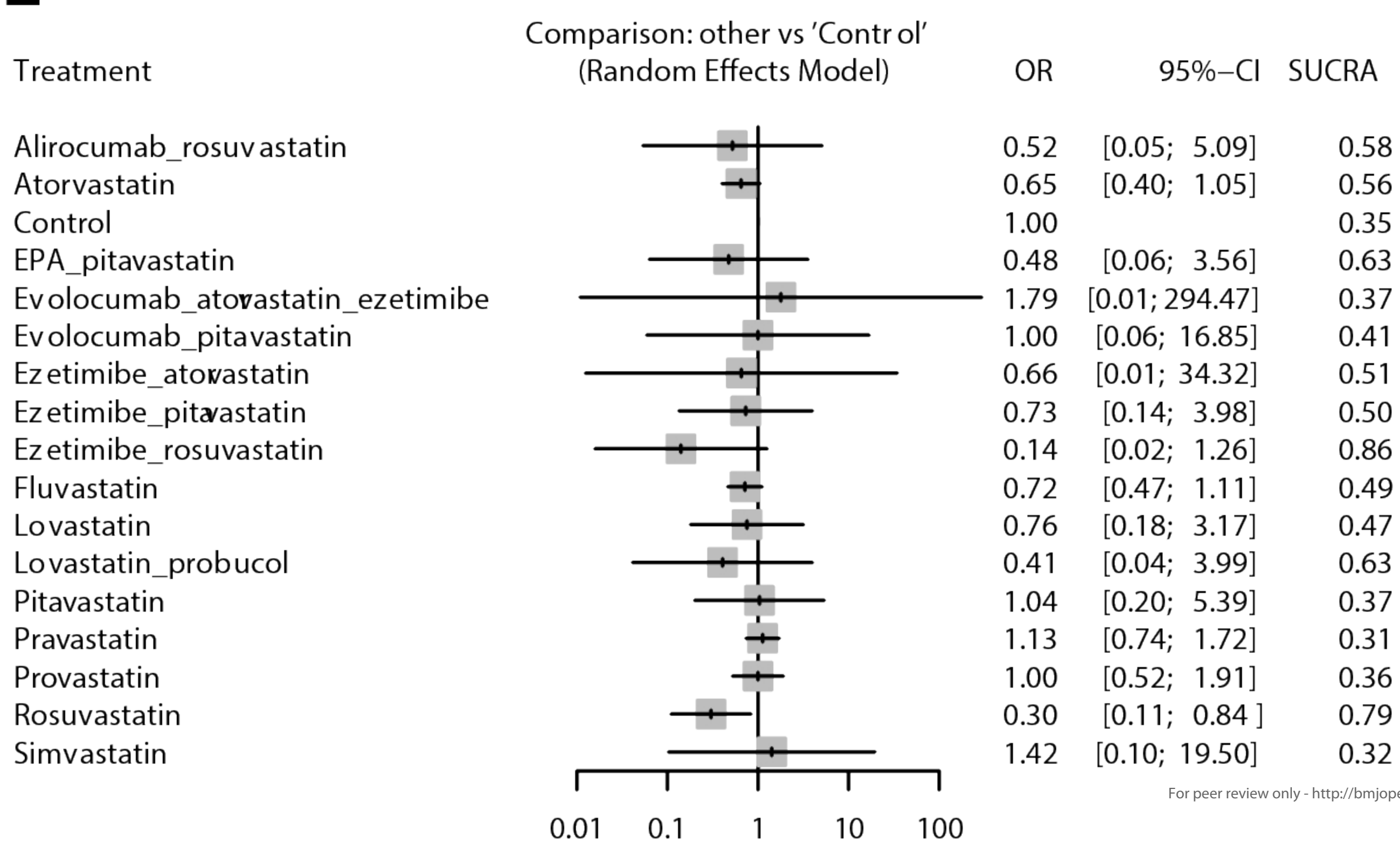
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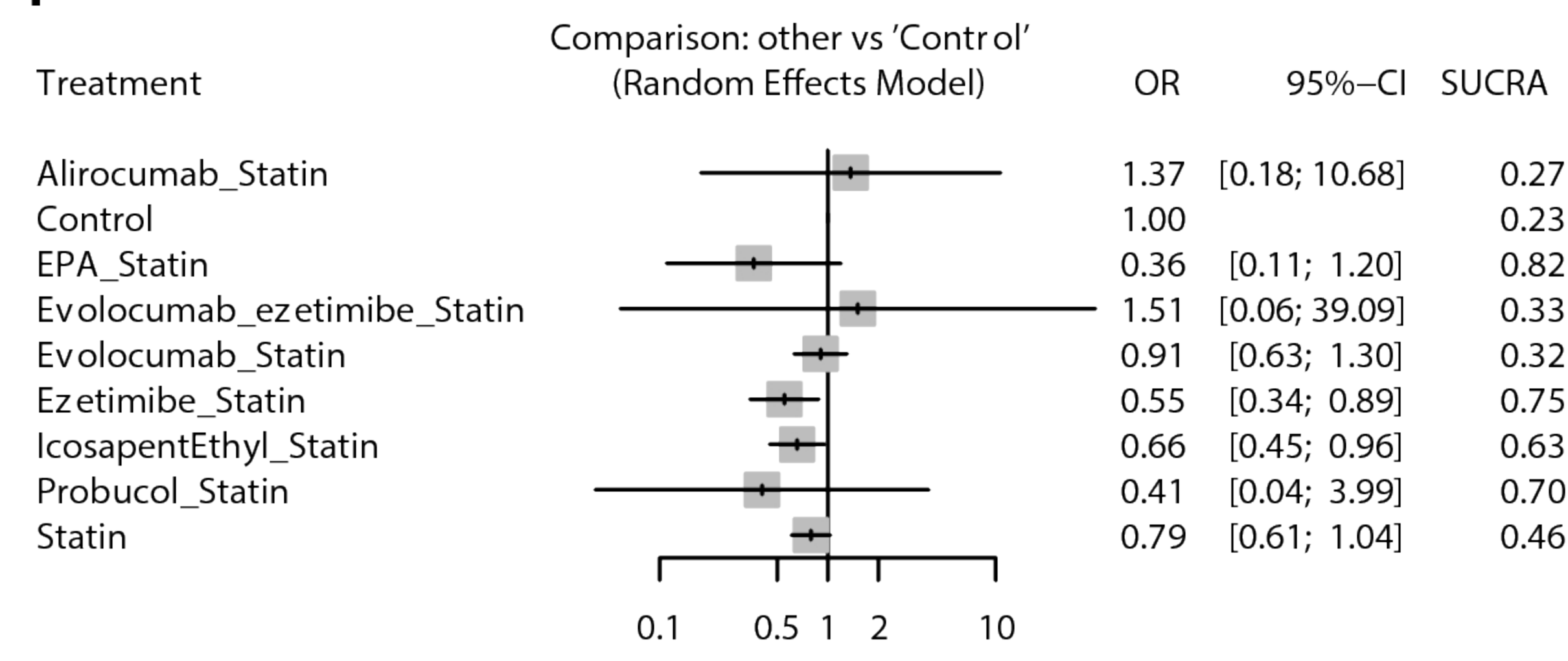
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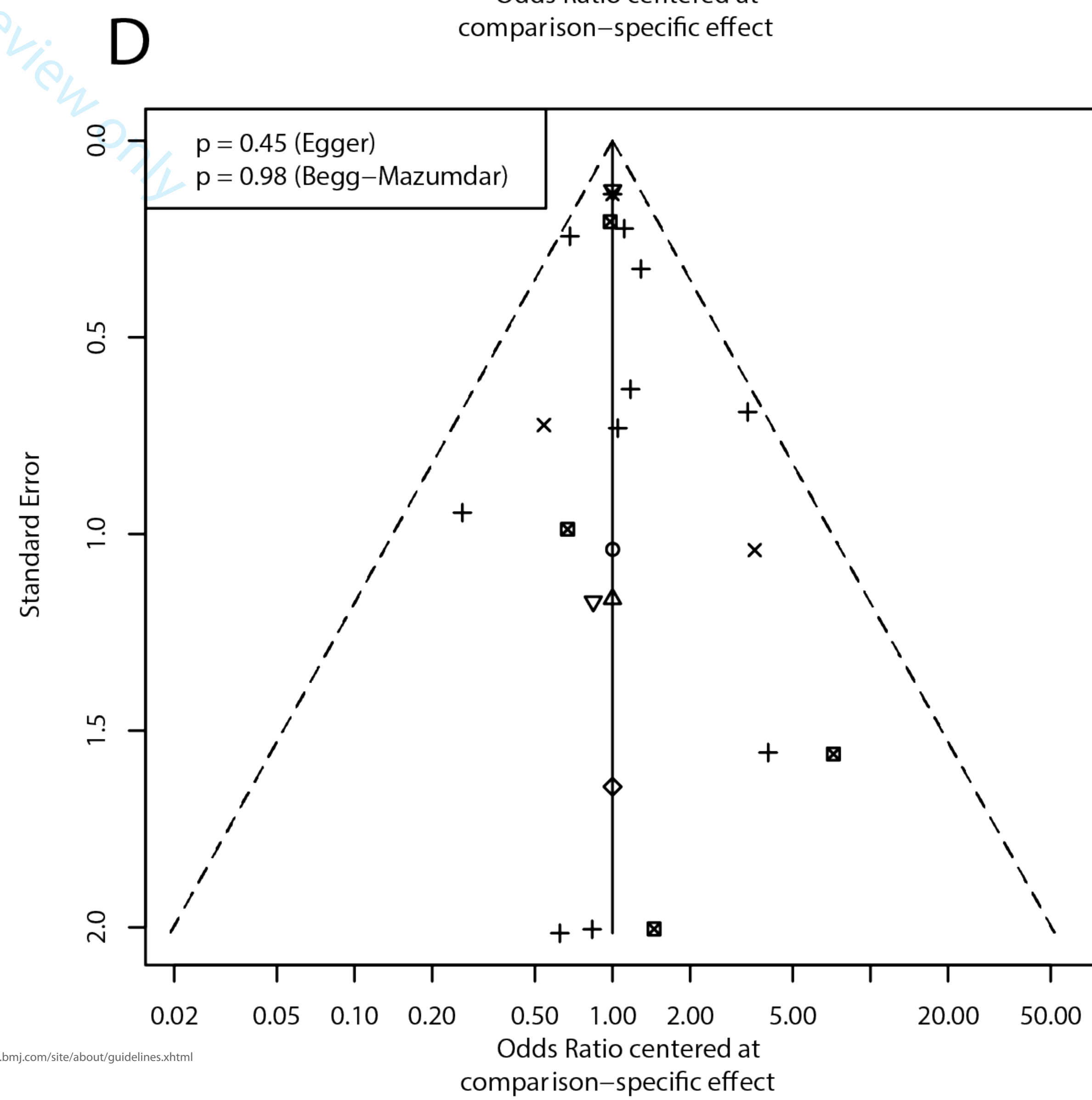
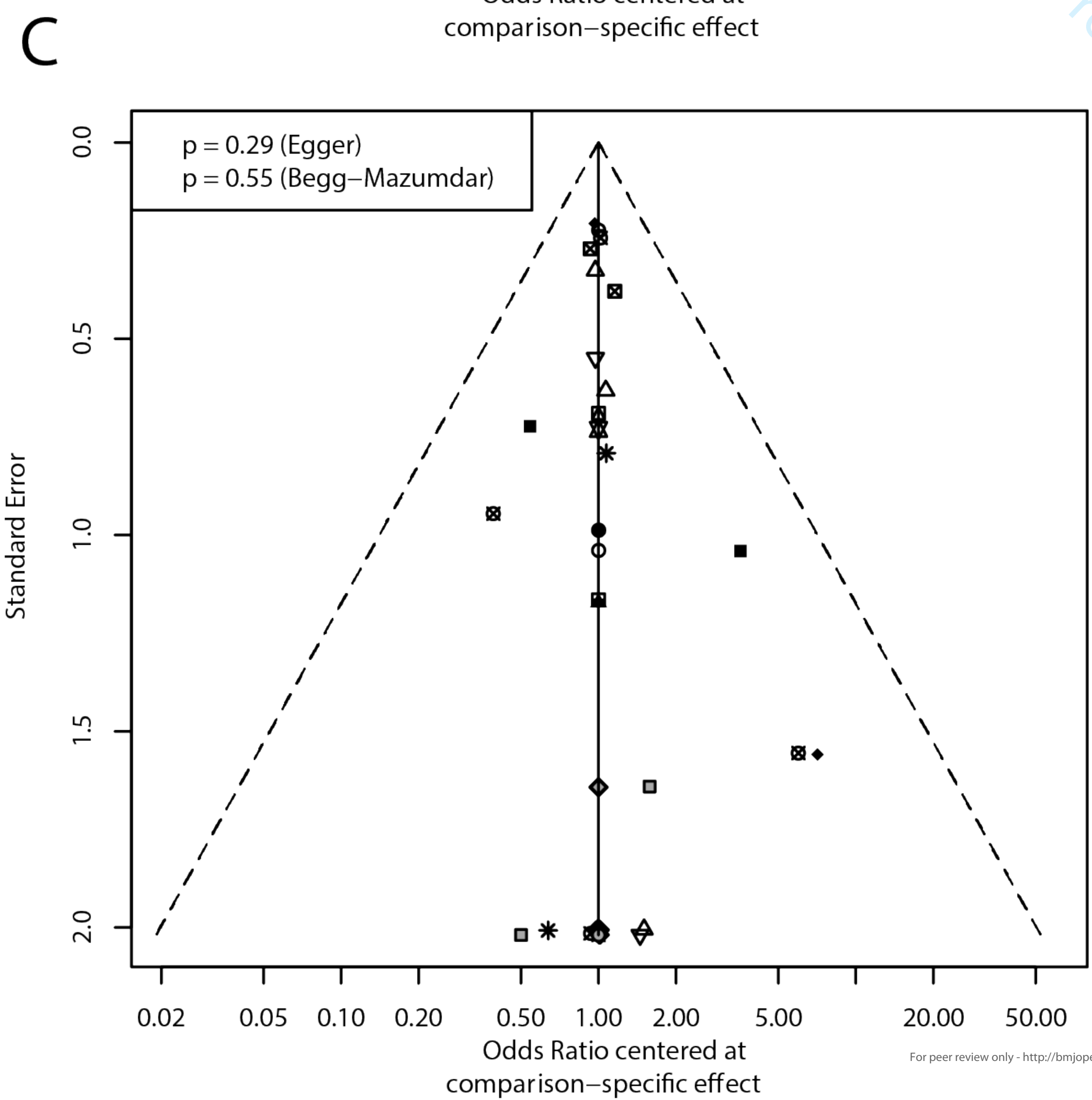
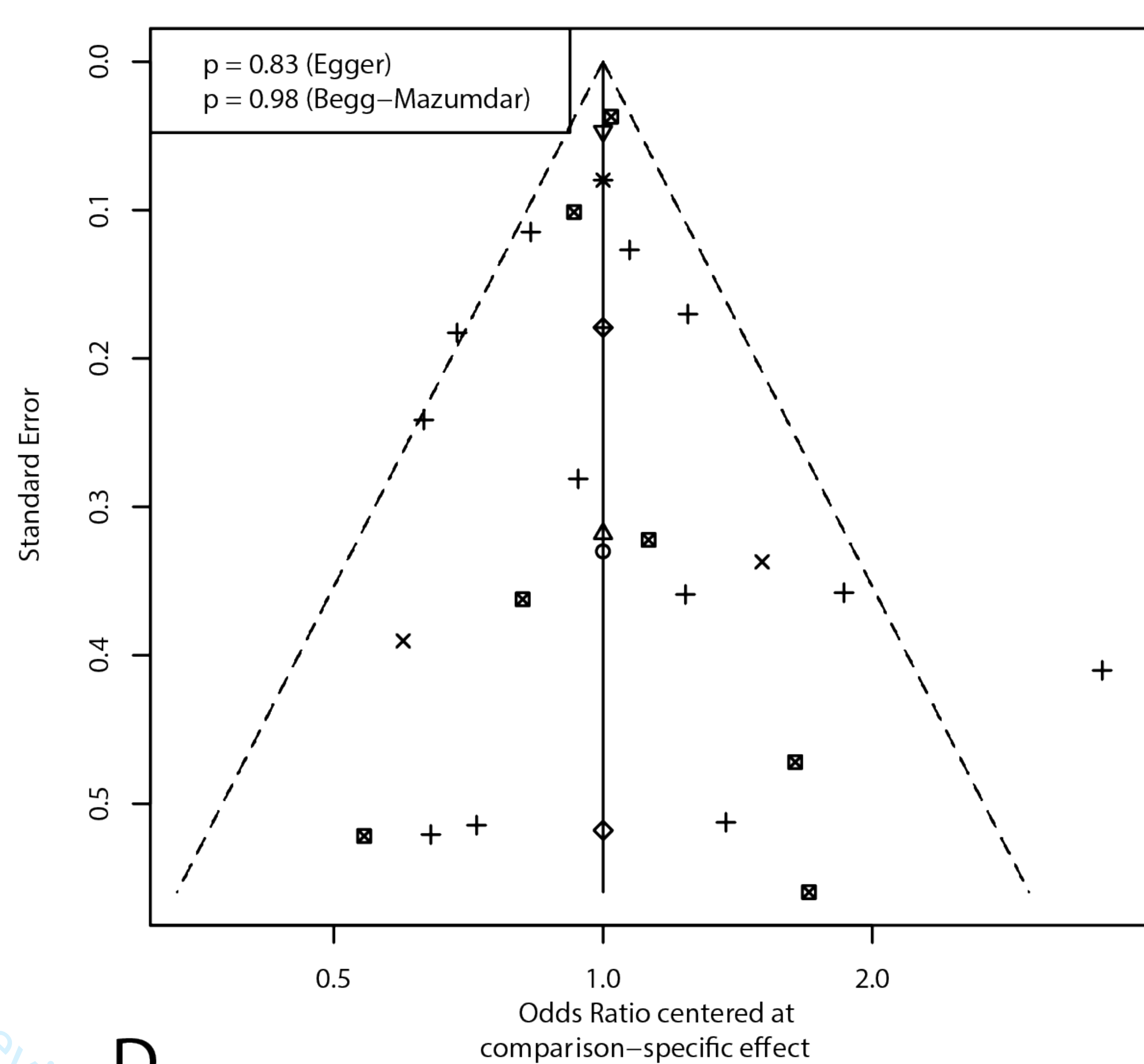
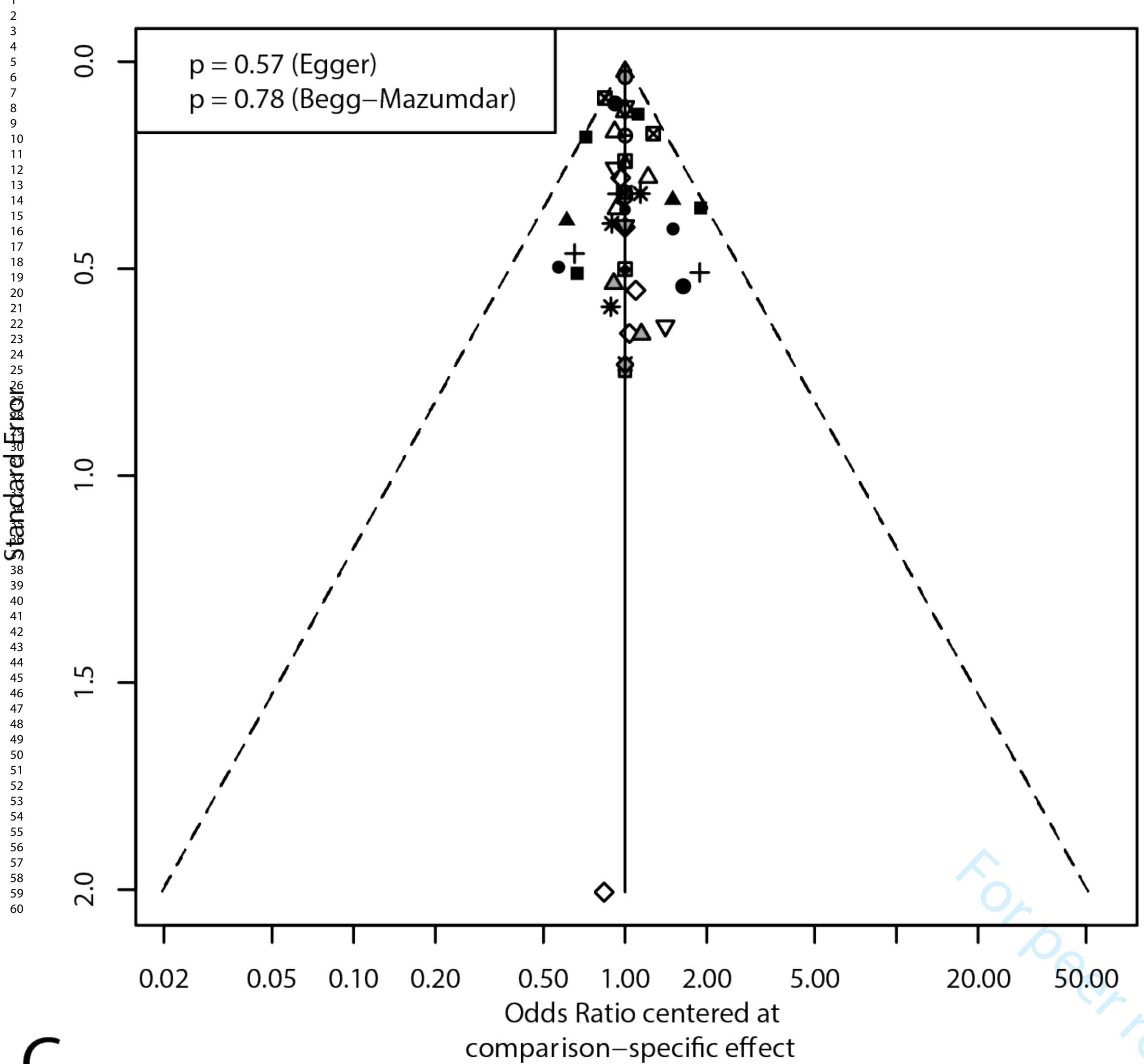
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PRISMA 2020 Checklist

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

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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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4 **1 Effectiveness of lipid-lowering therapy on mortality and**
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6 **2 major adverse cardiovascular event outcomes in patients**
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9 **3 undergoing percutaneous coronary intervention: a network**
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11 **4 meta-analysis of randomized controlled trials**

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42 **16 Abstract**

43
44 **17 Background**

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47 Emergency percutaneous coronary intervention (PCI) can quickly restore myocardial
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50 perfusion after acute coronary syndrome (ACS). Whether and which lipid-lowering
51
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53 regimens are effective in reducing major adverse cardiovascular events (MACEs) and
54
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56 mortality risk after PCI remain unclear.

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23 **Objective**

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

26 **Methods**

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

32 **Results**

33 Thirty-nine RCTs were included. For MACEs, alirocumab plus rosuvastatin (OR:
34 0.18; 95% CI: 0.07-0.44;), evolocumab plus ezetimibe and statins (OR: 0.19; 95%
35 CI:0.06-0.59), eicosapentaenoic acid (EPA) plus pitavastatin (HR: 0.67; 95% CI:
36 0.49-0.96), and icosapent ethyl plus statins (HR: 0.73; 95% CI: 0.62-0.86) had
37 significant advantages and relatively high rankings. For mortality, rosuvastatin (OR:
38 0.30; 95% CI: 0.11-0.84), ezetimibe plus statins (OR: 0.55; 95% CI: 0.43-0.89) and
39 icosapent ethyl plus statins (OR: 0.66; 95% CI: 0.45-0.96) had significant advantages
40 compared to the control.

41 **Conclusion**

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

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4 45 **Key words:**lipid-lowering therapy, major adverse cardiovascular events, mortality,
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6 46 network meta-analysis
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10 49 **Introduction**

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12
13 50 Acute coronary syndrome (ACS) is a term used to refer to a range of conditions
14
15 51 associated with acute myocardial ischemia and/or infarction, which are usually due to
16
17 52 coronary artery occlusion and acute ischemic necrosis of the myocardium due to
18
19 53 progression of coronary atherosclerotic lesions(1-2).Emergency percutaneous
20
21 54 coronary intervention (PCI) can quickly restore myocardial perfusion(3). Although
22
23 55 the development of technological and procedural PCI have resulted in substantial
24
25 56 improvements in clinical outcomes, recurrent coronary events may still occur after
26
27 57 PCI(4).

28
29 58 The view of "residual cardiovascular risk" was introduced because MACE still occurs
30
31 59 in some patients who received PCI during follow-up. PCI can treat focal
32
33 60 manifestations of systemic progressive disease, but the residual risk of acute coronary
34
35 61 syndrome is largely related to the systemic proatherosclerotic effect of poorly
36
37 62 controlled cardiovascular risk factors(5). Lowering lipid levels, especially LDL-C,
38
39 63 can halt the progression of coronary atherosclerosis and improve cardiovascular
40
41 64 outcomes. Based on this view, it is believed that long-term optimal lipid-lowering
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43 65 therapy is effective in reducing long-term cardiovascular events after PCI. However,
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45 66 the view was still subject to challenges.
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4 68 Based on data from the “Korea Acute Myocardial Infarction Registry”, the proponents
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6 69 concluded that patients treated with statins had significantly lower rates of MACE,
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9 70 all-cause death, and cardiac death during the 2-year follow-up period after PCI
10
11 71 application(6). However, a study of postoperative follow-up of PCI patients enrolled
12
13
14 72 in the Melbourne Interventional Group registry concluded that statins have no
15
16
17 73 significant benefit to MACEs after PCI(6). The controversy may be based on two
18
19
20 74 reasons: on the one hand, is that the optimal lipid reduction target may not be
21
22
23 75 achieved by using single statins(7,8). On the other hand, long-term high-dose
24
25 76 application of statins increases the risk of intracerebral hemorrhage and other side
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28 77 effects(9,10).

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30 78
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32 79 There is a consensus on preloading high-dose statins to reduce MACEs in the
33
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35 80 perioperative period with PCI(11,12). However, there is still insufficient evidence for
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38 81 the continued application of lipid-lowering drugs to reduce the risk of long-term
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41 82 MACE and mortality. This study will assess the benefits of different lipid-lowering
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44 83 regimens on the risk of MACEs and mortality in the post-PCI population by network
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46
47 84 meta-analysis.

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49 86 **Methods**

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53 87 This study was performed in accordance with Preferred Reporting Items for
54
55
56 88 Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study was
57
58
59 89 registered with PROSPERO (CRD 42018099600).

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4 90 **Patient and Public Involvement**

5
6 91 None

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11 93 **Search strategy**

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14 94 Public literature databases, including PubMed, Embase, and the Cochrane Library,
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16
17 95 were searched from inception to August 2022 without language restrictions using the
18
19
20 96 following search terms: (lipid-lowering or statin or simvastatin or rosuvastatin or
21
22 97 atorvastatin or fluvastatin or lovastatin or pravastatin or pitavastatin or mevastatin or
23
24 98 ezetimibe or “eicosapentaenoic acid” or “icosapent ethyl” or “bempedoic acid” or
25
26 99 fibrate or bezafibrate or gemfibrozil or fenofibrate or ciprofibrate or evolocumab or
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28
29 100 alirocumab or evinocumab or volanesorsen or vupanorsen or pelacarsen or olezarsen
30
31
32 101 or inclisiran or olpasiran) and (“percutaneous coronary intervention” or “coronary
33
34 102 angioplasty”) and (random* or randomized or randomized). The references of
35
36
37 103 relevant systematic reviews and meta-analyses were also searched to avoid omissions.
38
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40 104 The two authors conducted literature retrieval independently, and any conflicts were
41
42
43 105 resolved through discussion with the third author.
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48 107 **Inclusion and exclusion criteria**

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51 108 The literature was included if it met the following criteria: 1, the study adopted a
52
53 109 randomized controlled study design; 2, the study included patients who received PCI
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56 110 surgery or reported the subgroup of the population that received PCI; 3, the lipid-
57
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59 111 lowering regimen was applied to the population of the intervention group; 4, the
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4 112 control group used a different lipid-lowering agent or regimen; and 5, the study
5
6 113 reported the outcome of mortality and/or MACE. Exclusion criteria: 1, as preloading
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9 114 of statins before PCI had clear benefits, to determine whether application of lipid-
10
11 115 lowering drugs after PCI also had beneficial effects. This work excluded the study on
12
13 116 the preloading application of lipid-lowering drugs before PCI; 2, although high-dose
14
15 117 lipid-lowering agents, such as statins, have a better lipid-lowering effect, long-term
16
17 118 application may bring potential side effects(9-13). In this study, all agents were
18
19 119 considered to be applied with reasonable doses, and dose–response studies were
20
21 120 excluded. In addition, repeatedly published studies, protocols, conference abstracts,
22
23 121 reviews, comments and editorials were also excluded.
24
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32 123 Data extraction and quality assessment
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34

35 124 Two authors independently extracted the information from the included studies. The
36
37 125 contents include the name of the first author, publication year, study location, sample
38
39 126 size (population received PCI), study abbreviation and registration number, lipid-
40
41 127 lowering intervention and control, and follow-up time.
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48 129 The outcomes analyzed were the incidence of all-cause mortality and MACE, whether
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50 130 reported as dichotomous or hazard ratio (HR) statistics based on Cox regression. The
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52 131 MACE outcome was selected to most closely approximate the composite endpoint,
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54 132 including mortality, MI, stroke, coronary revascularization, and restenosis. Study
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56 133 quality was assessed by two investigators using the Cochrane risk of bias assessment
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4 134 tool, which included random sequence generation, allocation concealment, blinding of
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6 135 participants and personnel, blinding of outcome assessment, incomplete outcome data,
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9 136 selective reporting, and other potential biases.
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14 138 Statistical analysis

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17 139 For each direct paired comparison, we used the odds ratios and their 95% confidence
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19 140 intervals (CIs) for dichotomous outcomes. The hazard ratios and their 95% CIs based
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21
22 141 on Cox regression results were also pooled for reporting. We conducted frequentist
23
24 142 network meta-analysis (NMA) using random effect models with restricted maximum
25
26
27 143 likelihood estimation to quantify network heterogeneity. The Q statistic was used to
28
29
30 144 assess the sum of statistics for heterogeneity (within designs) and for overall
31
32
33 145 inconsistency (between designs)⁽¹⁴⁾. The ranking probabilities of each regimen were
34
35 146 estimated using the surface under the cumulative ranking curve (SUCRA), and a
36
37
38 147 comparison-adjusted funnel plot was used to examine potential publication biases in
39
40
41 148 NMA. P values of less than 0.05 were considered to be statistically significant. The
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43 149 NMA was performed using R language with the “netmeta” package.
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47 48 151 **Results**

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51 152 After removing duplications, we obtained 1588 literature items. After a screen of the
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53 153 titles and abstracts, 1515 irrelevant studies were excluded. Seventy-three articles were
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56 154 screened for full text. The following articles were excluded: dose–response studies
57
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59 155 (8), no PCI population or subgroup was reported (6); no mortality or MACE-related
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4 156 outcomes were reported (6); repeated publication (5); study related to preloading of
5
6 157 lipid-lowering agents (4); study not related to lipid-lowering agents (3); protocol (1);
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9 158 non-RCT design (1). Finally, 39 articles were included containing 54478 patients after
10
11 159 PCI(15-53) (Figure 1).
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161 Among the included studies, the publication period ranged from 1991 to 2022. The
162 research locations were mainly in Asia (China, Japan and South Korea), Europe
163 (Netherlands, France, and Italy), America, and multiple centers. There were 10 studies
164 with sample sizes greater than 1000 patients. There were also 22 studies with publicly
165 available clinical study registration numbers (Table 1). In terms of design quality, all
166 included studies were RCTs. Therefore, the design quality is generally high. The main
167 factors potentially affecting design quality were the blinding of participants and
168 personnel and blinding of outcome assessment (Figure 2). However, as the desired
169 outcomes were mortality and MACE, the subjective factors of the investigator had
170 little influence on the outcomes.
171

171 **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	UMIN000000428	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	Pravastatin	2Y
Han Yaling 2009 [41]	China	1275	-	NCT00405717	Atorvastatin	Pravastatin	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]	Netherlands	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	-	Probuco;lovastatin	Placebo	6M
Haruhiko Onaka 1994 [52]	Japan	66	-	-	Pravastatin	Control	5M
Rakesh Sahni 1991 [53]	US	157	-	-	Lovastatin	Control	6M

172

173 Abbreviations: EPA: eicosapentaenoic acid.

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

175 As two studies did not specify the types of statins, the network meta-analysis will
 176 be divided into two parts. One part was analyzed based on specific types of statins,
 177 and the other was based on taking statins as a whole. For the dichotomous results of
 178 MACE, the NMA based on specific types of statins included 18 lipid-lowering
 179 regimens. The Q test for heterogeneity was $p = 0.07$, and for inconsistency, it was $p =$
 180 0.16 , indicating no evidence for heterogeneity and inconsistency in the NMA.

181 In pairwise comparisons with the control, alirocumab plus rosuvastatin (OR: 0.18;
 182 95% CI: 0.07-0.44; SUCRA: 0.94), evolocumab plus atorvastatin and ezetimibe (OR:
 183 0.18; 95% CI: 0.05-0.63; SUCRA: 0.90), ezetimibe plus rosuvastatin (OR: 0.29; 95%
 184 CI: 0.11-0.76; SUCRA: 0.80) have significant advantages and relatively high SUCRA
 185 rankings. No potential publication bias was found according to the comparison-
 186 adjusted funnel plot (Figure 3).

187

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

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4 191 ethyl plus statins (OR: 0.39; 95% CI: 0.25-0.62; SUCRA: 0.72) have significant
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6 192 advantages and relatively high SUCRA rankings. No potential publication bias was
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9 193 found.

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14 195 For the HR results of MACEs, the NMA based on specific types of statins included
15
16 196 nine regimens. The Q test for heterogeneity was $p = 0.964$ and because the network
17
18 197 comparisons lack loops. Therefore, the results were considered consistent. Compared
19
20 198 to the control, eicosapentaenoic acid (EPA) plus pitavastatin (HR: 0.67; 95% CI:
21
22 199 0.49-0.96; SUCRA: 0.91), atorvastatin (HR: 0.76; 95% CI: 0.63-0.90; SUCRA: 0.83),
23
24 200 and varespladib plus atorvastatin (HR: 0.77; 95% CI: 0.61-0.97; SUCRA: 0.77) have
25
26 201 significant advantages and relatively high SUCRA rankings. Potential publication bias
27
28 202 was not analyzed due to a smaller number of included studies.
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37 204 In the NMA based on taking statins as a whole, seven regimens were analyzed. EPA
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39 205 plus statins (HR: 0.60; 95% CI: 0.42-0.85; SUCRA: 0.96) and icosapent ethyl plus
40
41 206 statins (HR: 0.73; 95% CI: 0.62-0.86; SUCRA: 0.81) had significant advantages over
42
43 207 the control.
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50 209 For the dichotomous results of mortality, the NMA based on specific types of statins
51
52 210 included 17 lipid-lowering regimens. The Q test for heterogeneity was $p = 0.78$, and
53
54 211 for inconsistency, it was $p = 0.99$. Due to the rare occurrence of events, the results of
55
56 212 the comparison were low precision with a large standard error. Compared to the
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4 213 control, only rosuvastatin (OR: 0.30; 95% CI: 0.11-0.84; SUCRA: 0.79) showed a
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6 214 significantly better effect. Ezetimibe plus rosuvastatin had a relatively high SUCRA
7
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9 215 ranking, but there was no significant difference compared to the control (OR: 0.14;
10
11 216 95% CI: 0.02-1.26; SUCRA: 0.86). No potential publication bias was found (Figure
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14 217 4).

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19 219 In the NMA based on taking statins as a whole, nine regimens were analyzed.
20
21
22 220 Ezetimibe plus statins (OR: 0.55; 95% CI: 0.43-0.89; SUCRA: 0.75) and icosapent
23
24 221 ethyl plus statins (OR: 0.66; 95% CI: 0.45-0.96; SUCRA: 0.63) had significant
25
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27 222 advantages compared with the blank control group. No potential publication bias
28
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30 223 existed. NMA analysis was not performed due to the small number of studies
31
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33 224 reporting HR for mortality (Figure 5).

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36 37 226 **Discussion**

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40 227 This study analyzed the benefits of lipid-lowering therapy on mortality and MACE
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43 228 outcomes in patients who received PCI by network meta-analysis. The results showed
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46 229 that several lipid-lowering regimens could reduce the risk of MACEs compared with
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48
49 230 the blank control. Icosapent ethyl plus statins had the benefit of reducing both the risk
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52 231 of MACEs and mortality. However, EPA plus statins had more advantages in
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55 232 reducing the risk of MACEs. Of note, based on the current evidence, alirocumab and
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58 233 evolocumab plus statins had obvious advantages in reducing the risk of MACEs but
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60 234 had no obvious benefit in reducing the risk of mortality.

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6 236 EPA is a long-chain omega-3 polyunsaturated fatty acid. Long-term intake of EPA
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9 237 can reduce the residual cardiovascular risk to reduce the risk of MACEs(54). In terms
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11 238 of pathological mechanisms, EPA combined with pitavastatin can reduce the lipid
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13 239 volume of coronary artery plaque and total atherosclerotic plaque volume in patients
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16 240 who receive PCI, which may be the reason for the reduced risk of MACEs(55).
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22 242 Icosapent ethyl is a highly purified and stable eicosapentaenoic acid ethyl ester that
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24 243 has potential higher anti-inflammatory, antioxidant, plaque stability and cell
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26 244 membrane stability effects(56). In the NMA results, icosapent ethyl plus statins had
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28 245 significant benefits for either mortality or MACEs in patients who received PCI,
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30 246 which was an ideal regimen for the population.
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37 248 Ezetimibe inhibits the absorption of cholesterol and has a synergistic lipid-lowering
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39 249 pharmacological effect with statins to further reduce the risk of death and MACE. In
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41 250 particular, when combined with rosuvastatin, it has a stronger lipid-lowering effect
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43 251 with a high safety profile without the risk of drug interactions(57). Our NMA results
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45 252 also showed that it can reduce the risk of MACE and mortality. According to the
46
47 253 guidelines for the management of dyslipidemia from the European Society of
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49 254 Cardiology and the European Atherosclerosis Society, ezetimibe was recommended if
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51 255 the LDL-C level was not reached(58,59). The American College of Cardiology
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53 256 guidelines also recommend adding ezetimibe when using maximally tolerated statin
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4 257 therapy and if LDL-C levels remain ≥ 70 mg/dL(60). These benefits have also been
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6 258 demonstrated in the secondary prevention of PCI.
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11 260 Alirocumab and evolumab are both proprotein convertase subtilisin/kexin type 9
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13 261 inhibitors (PCSK9i), which can increase the level of LDL receptor in the liver, thus
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15 262 improving the ability of the liver to bind LDL-C and reducing the level of peripheral
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17 263 LDL-C(61). There was also a synergistic lipid-lowering pharmacological effect when
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19 264 PCSK9i was combined with statins that significantly reduced LDL-C and
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21 265 atherosclerosis event risk; however, there was still controversy regarding the mortality
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23 266 risk reduction(62). It has been suggested that the powerful effect of PCSK9I on
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25 267 reducing LDL-C predisposes patients to hypocholesterolemia, which will not increase
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27 268 the risk of cerebral hemorrhage ,PCSK9i may be a preferred lipid-lowering agent in
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29 269 patients with elevated ICH risk(63,64). On the other hand, PCSK9i could not reduce
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31 270 serum inflammatory factors, suggesting that it may not reduce the risk of residual
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33 271 inflammation in the post-PCI population(65).
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45 273 In the results of this study, lipid-lowering therapy strategies had general advantages in
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47 274 reducing MACE risk. However, for all-cause mortality, the advantage of lipid-
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49 275 lowering therapy was not obvious. Based on dichotomous outcomes of mortality,
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51 276 some strategies may even have a tendency to increase the mortality risk. This
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53 277 challenges the opinion that lipid-lowering therapy is recommended after PCI(66). A
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55 278 large sample size retrospective study suggests that statins can reduce the risk of all-
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4 279 cause death in patients with coronary artery disease undergoing PCI, regardless of
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6 280 personal cholesterol levels(67). Alternatively, the “Lipid Paradox” view has been
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9 281 proposed and indicated that higher levels of LDL-C and triglycerides on admission
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11 282 are associated with better clinical outcomes. Especially in patients with ST-elevation
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14 283 myocardial infarction, lower LDL-C levels were associated with worse mortality
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17 284 outcomes(68). However, this view is also controversial(69).

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22 286 On the other hand, it is possible that the contribution of LDL-C reduction to the risk
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24 287 of mortality outcomes is obscured by the other confounding factors. For example,
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27 288 inflammatory status may also have an important impact on patient mortality risk. In a
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30 289 cohort of post-PCI patients with low LDL-C levels, residual inflammatory risk also
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32 290 had a significant effect on overall mortality(70). C-reactive protein can also predict
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35 291 long-term mortality in post-PCI patients independent of LDL-C levels(71). In
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38 292 addition, cardiac remodeling also has an important impact on the survival outcome of
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40 293 people after PCI(72).

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43 294 There are still several limitations in this study. First, this study was based on the study
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45 295 level instead of the individual level, making it difficult to consider the individual
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48 296 confounding factors in the analysis. Second, two included studies did not specify the
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51 297 type of statins, so our study had to be analyzed separately according to whether all
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53 298 statins were considered as a whole. Third, the criteria for defining MACEs varied
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56 299 among studies that contributed to heterogeneity among the study results. Fourth,
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58 300 many included studies reported only dichotomous outcomes but did not report the HR
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4 301 results, resulting in the incompleteness of the relevant analysis results.
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11 304 In conclusion, the results of this study suggest that EPA, especially icosapent ethyl,
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13
14 305 plus statins had a beneficial effect on reducing the risk of MACEs and mortality in
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17 306 post-PCI patients. PCSK9i plus statins was able to reduce the risk of MACEs, but the
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19 307 risk of mortality remained unclear.
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35
36 315 Ying Zheng guided the data analysis and the production of the figures, Xian-Geng

37
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41

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49
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54 326 **Declarations**

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58 328 **Ethics approval and consent to participate**

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3 329 This study does not involve human participants and ethical approval was not required.
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6
7 331 **Consent for publication**

8 332 not applicable.
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12 334 **Competing interests**

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17 336 **References**

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6 640 **Figure 1.** Flowchart of the study selection process for eligible studies
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9 641 **Figure 2.** Methodological quality assessment of included studies
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11 642 **Figure 3.** Network plots of comparisons for major outcomes included in the analyses.
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14 643 A: dichotomous results of MACE based on specific types of statins; B: dichotomous
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16 644 results of MACE based on taking statins as a whole; C: hazard ratio results of MACE
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18 645 based on specific types of statins; D: hazard ratio results of MACE based on taking
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20 646 statins as a whole; E: dichotomous results of mortality based on specific types of
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22 647 statins; F: dichotomous results of mortality based on taking statins as a whole.
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27 648 **Figure 4.** Forest plots of lipid-lowering therapy compare to control for outcomes in
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30 649 network meta-analysis with SUCRA ranking results. A: dichotomous results of
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32 650 MACE based on specific types of statins; B: dichotomous results of MACE based on
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34 651 taking statins as a whole; C: hazard ratio results of MACE based on specific types of
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36 652 statins; D: hazard ratio results of MACE based on taking statins as a whole; E:
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38 653 dichotomous results of mortality based on specific types of statins; F: dichotomous
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40 654 results of mortality based on taking statins as a whole.
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45 655 **Figure 5.** The comparison-adjusted funnel plot for assessing all main outcomes. A:
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48 656 dichotomous results of MACE based on specific types of statins; B: dichotomous
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50 657 results of MACE based on taking statins as a whole; C: dichotomous results of
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7 **684 Authors and Afliations**

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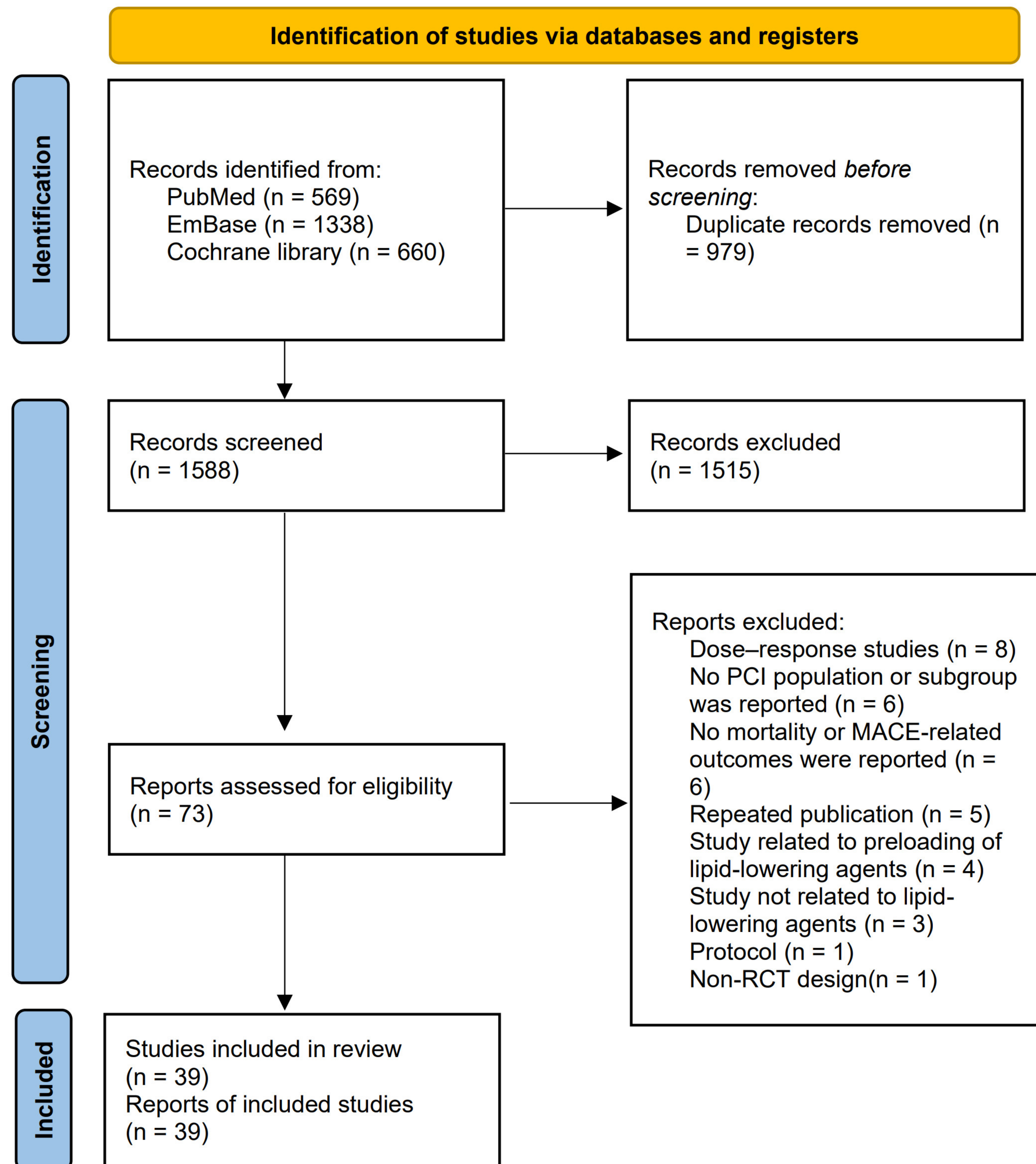
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PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



*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).

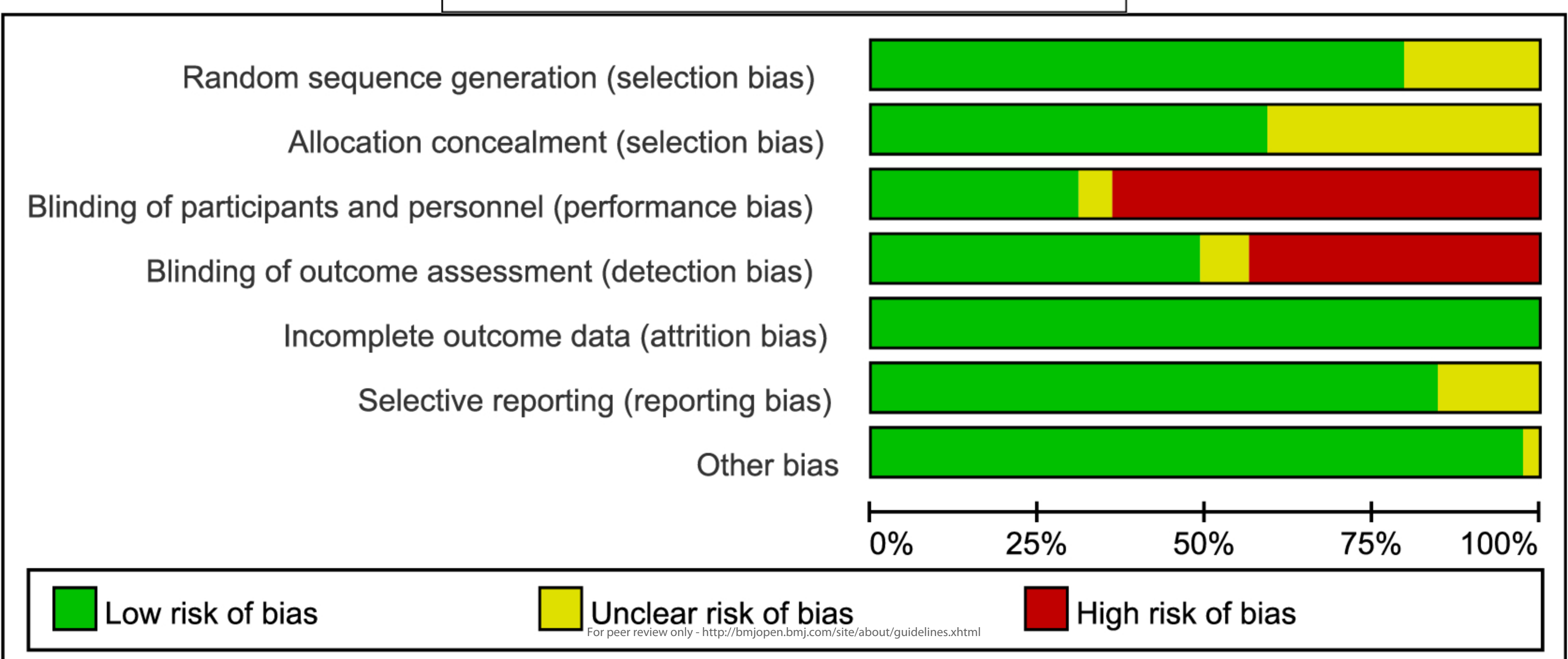
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

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

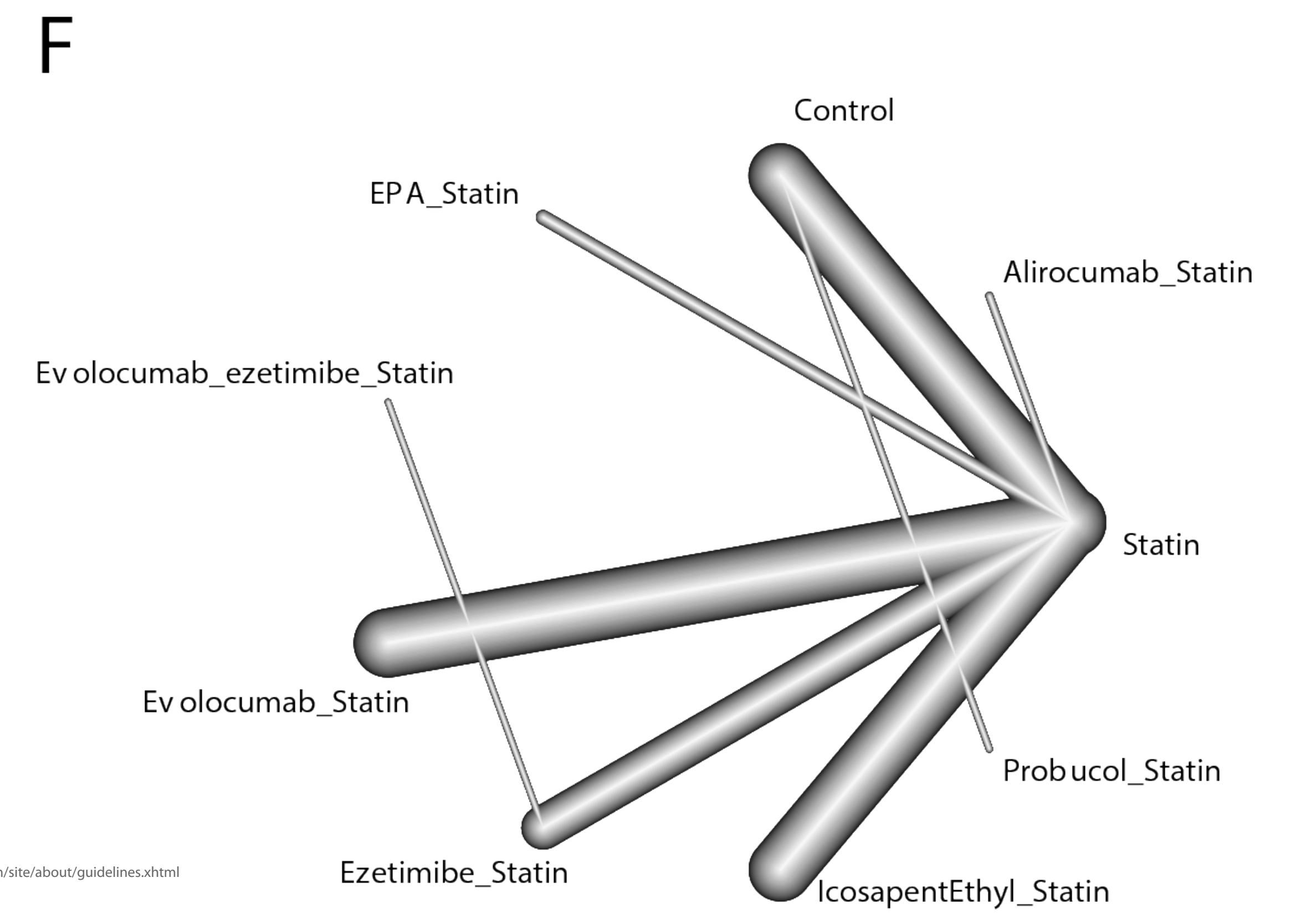
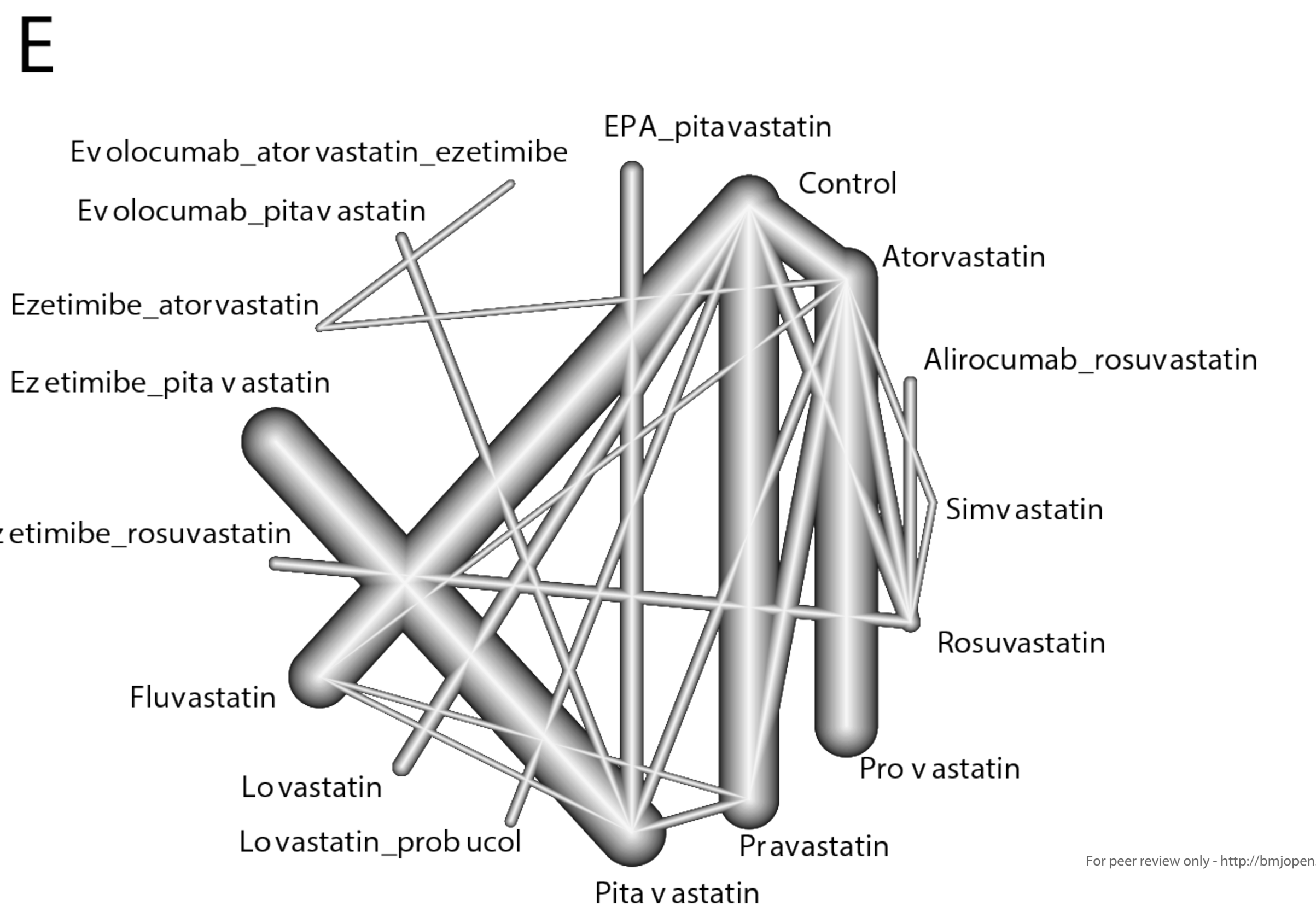
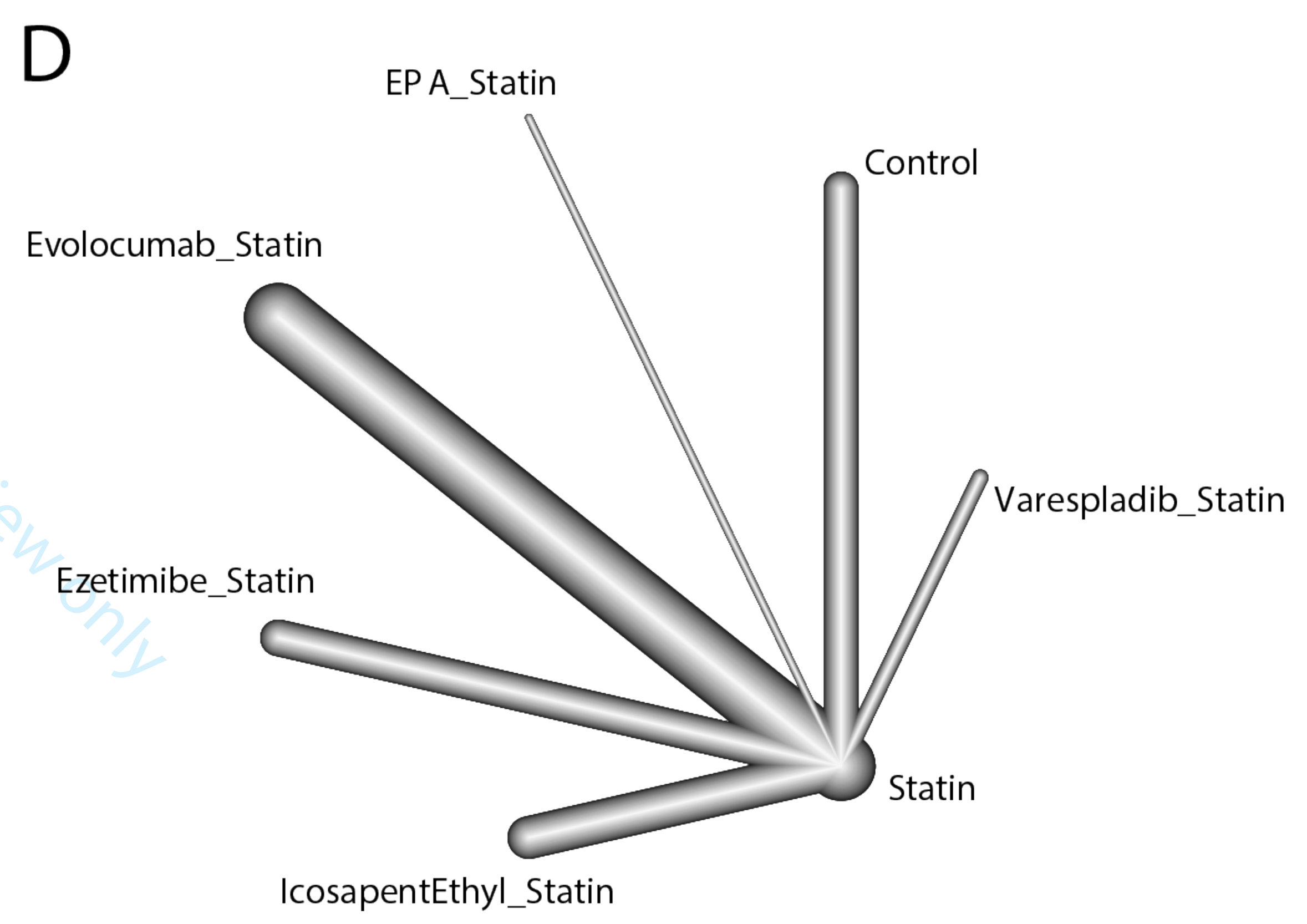
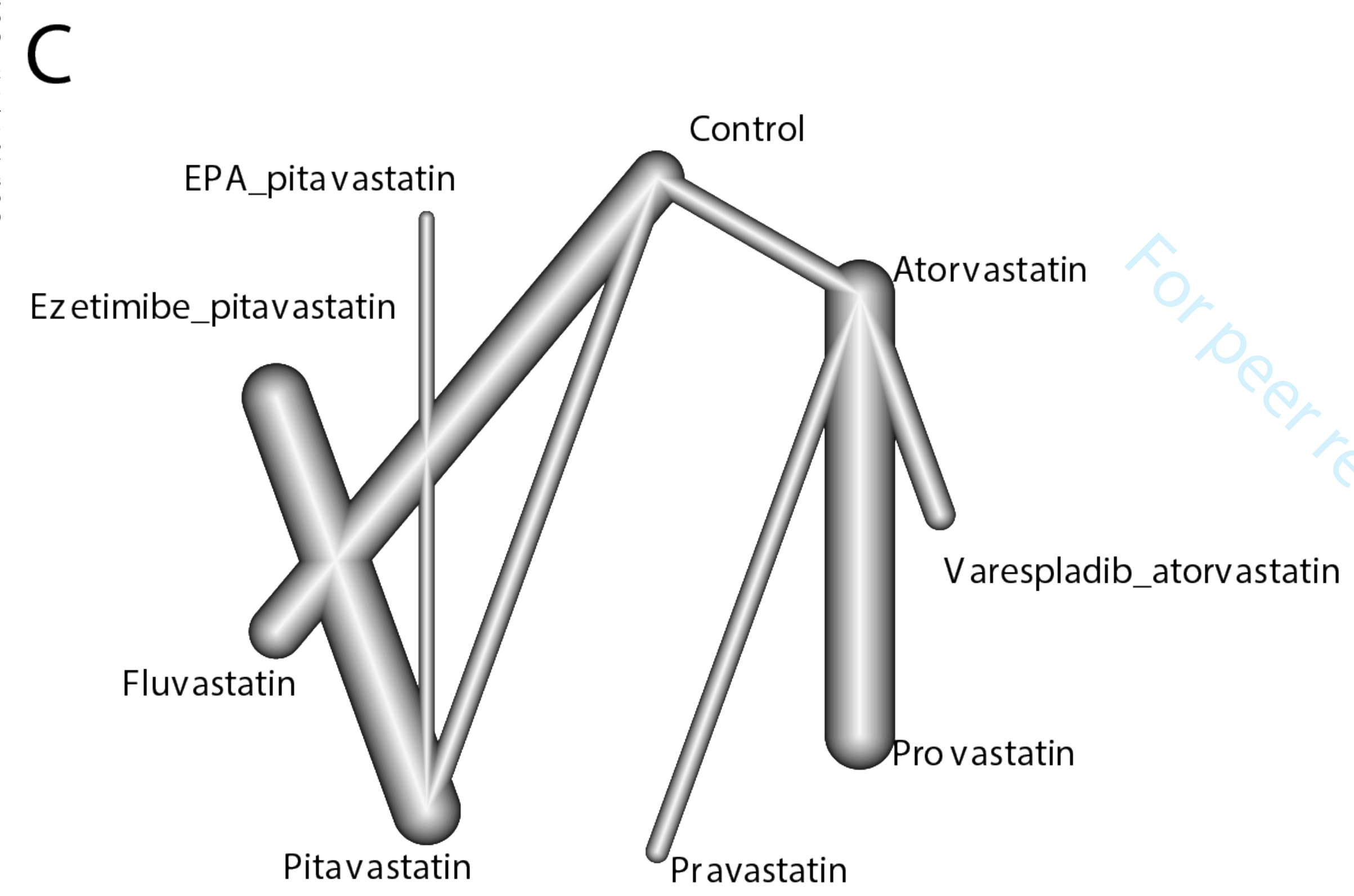
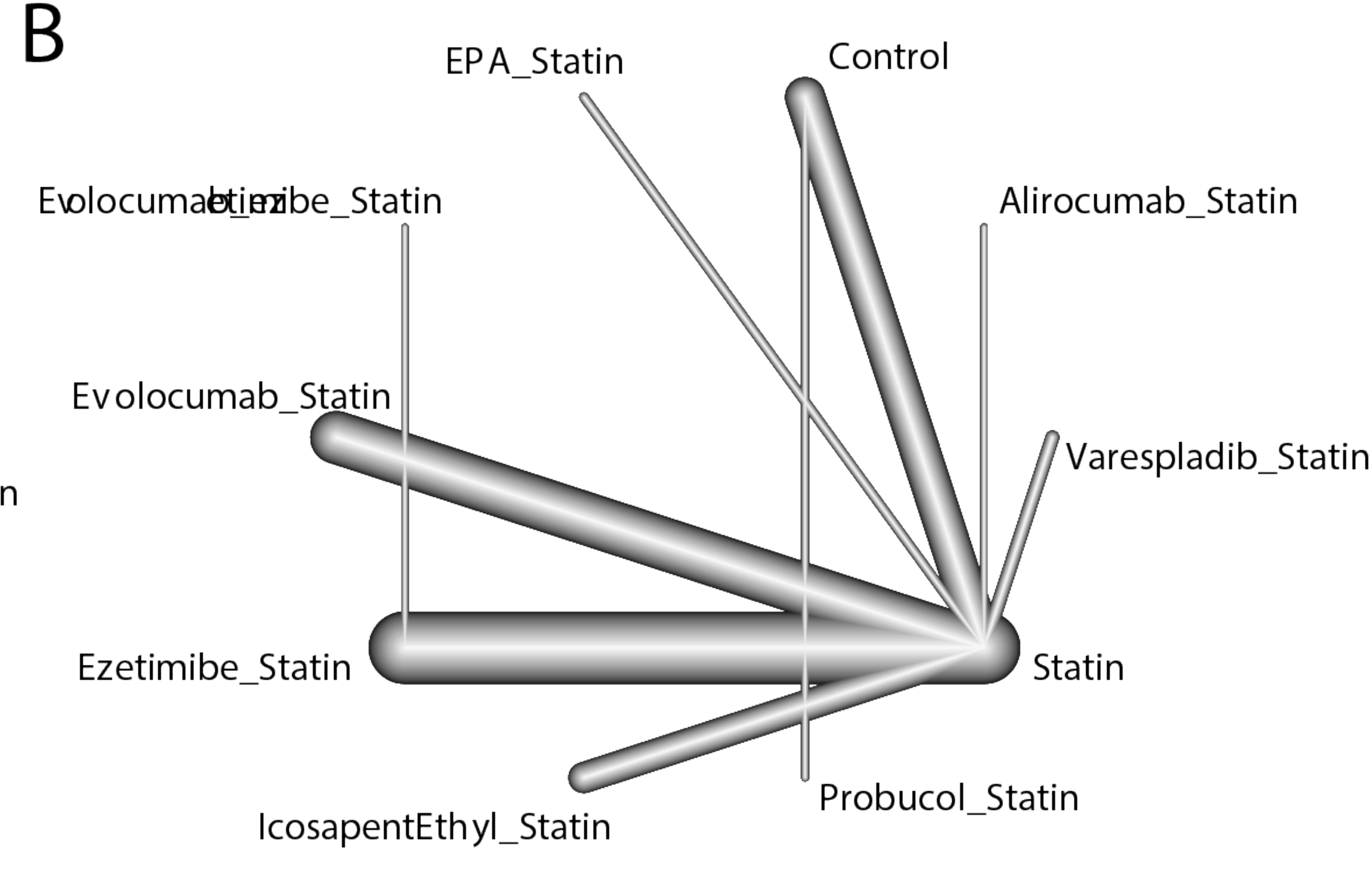
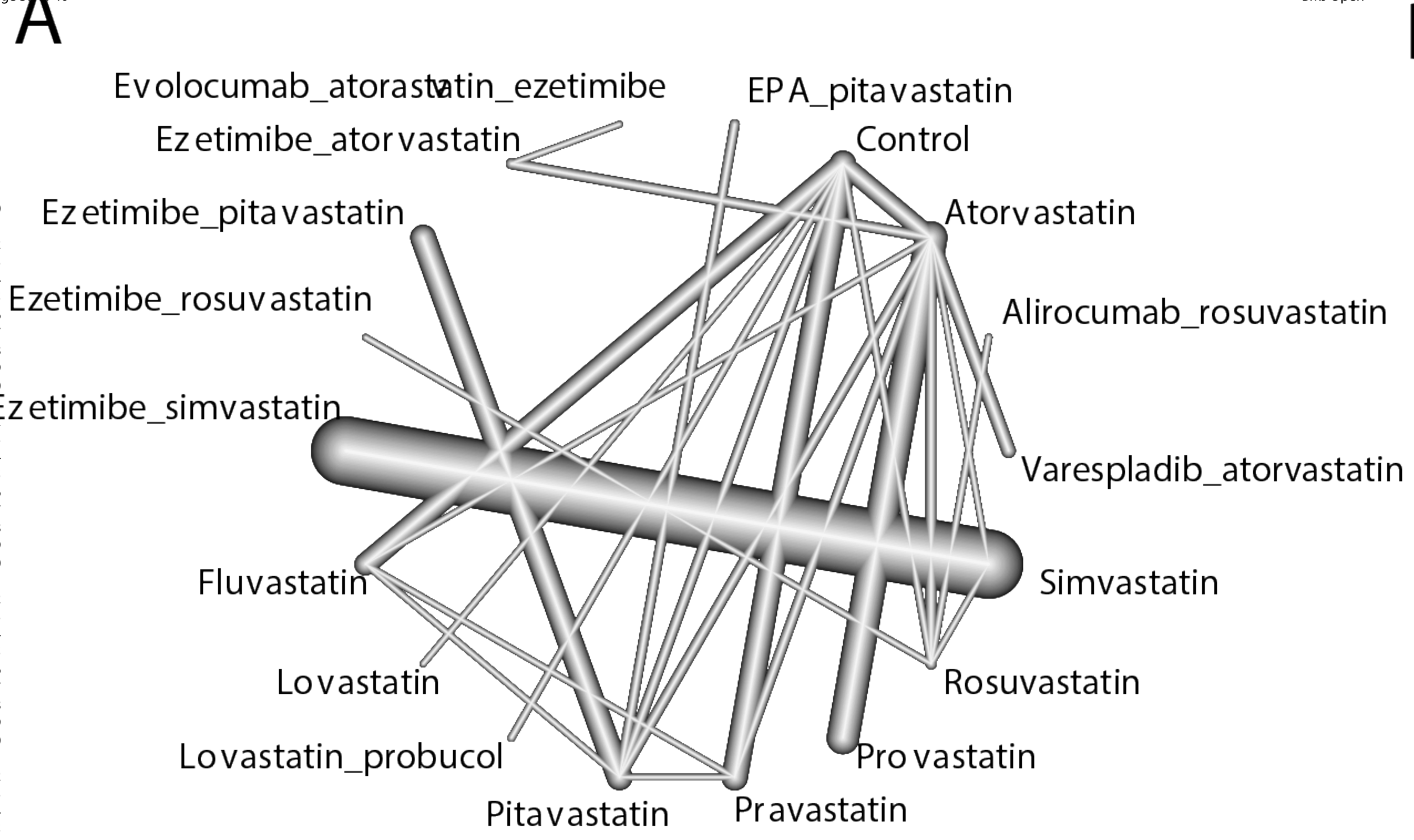
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	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (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	+	?	-	+	+	+	+
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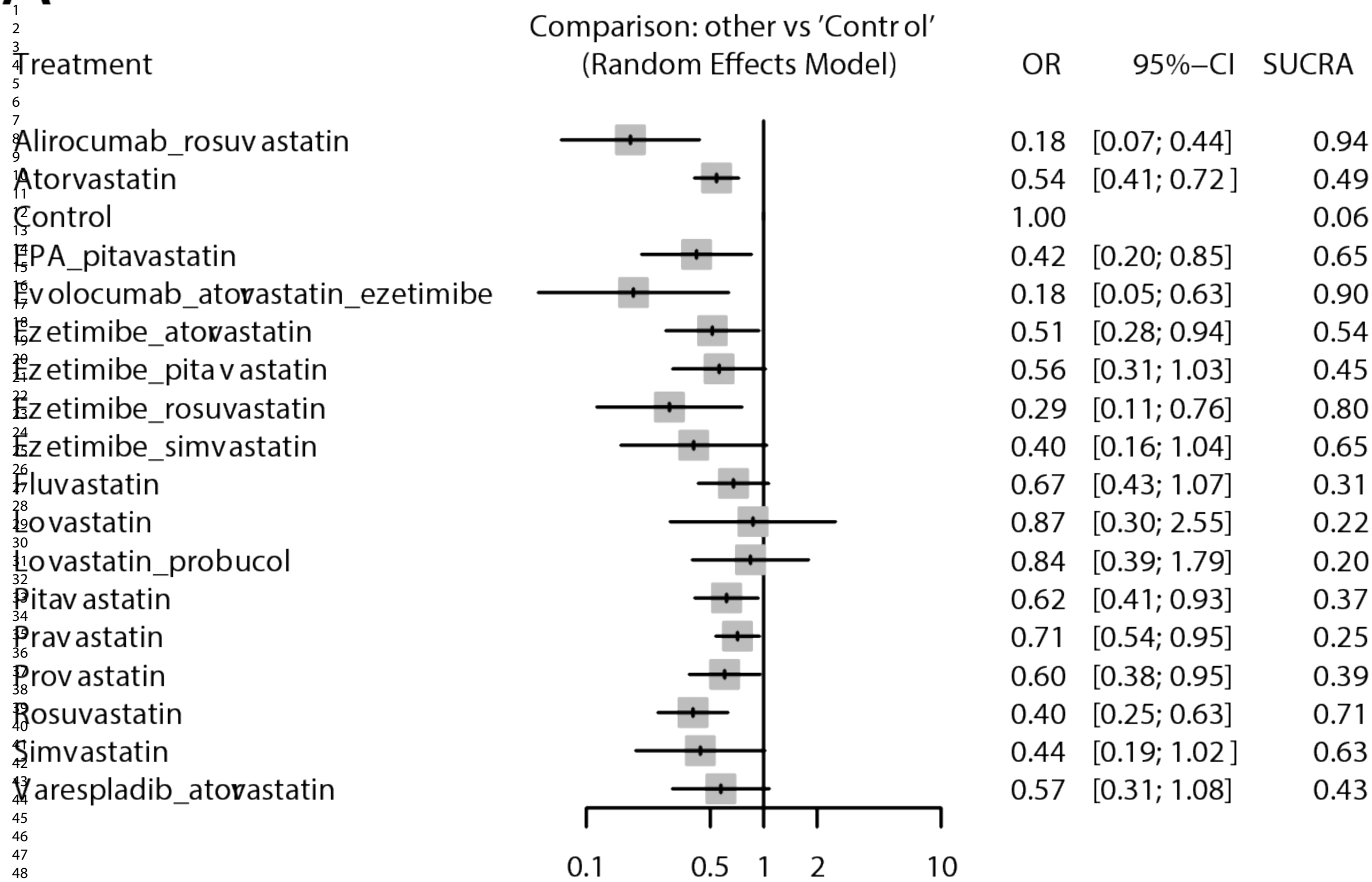


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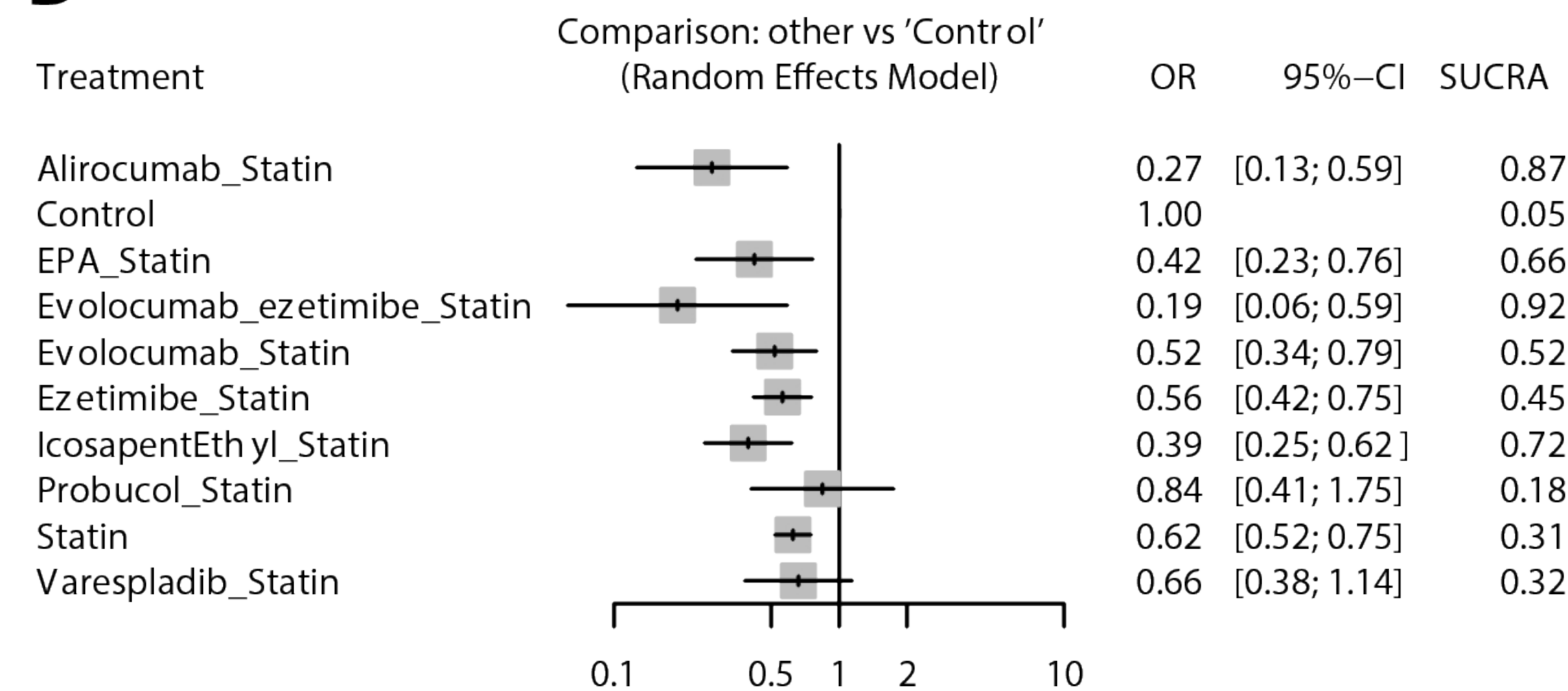


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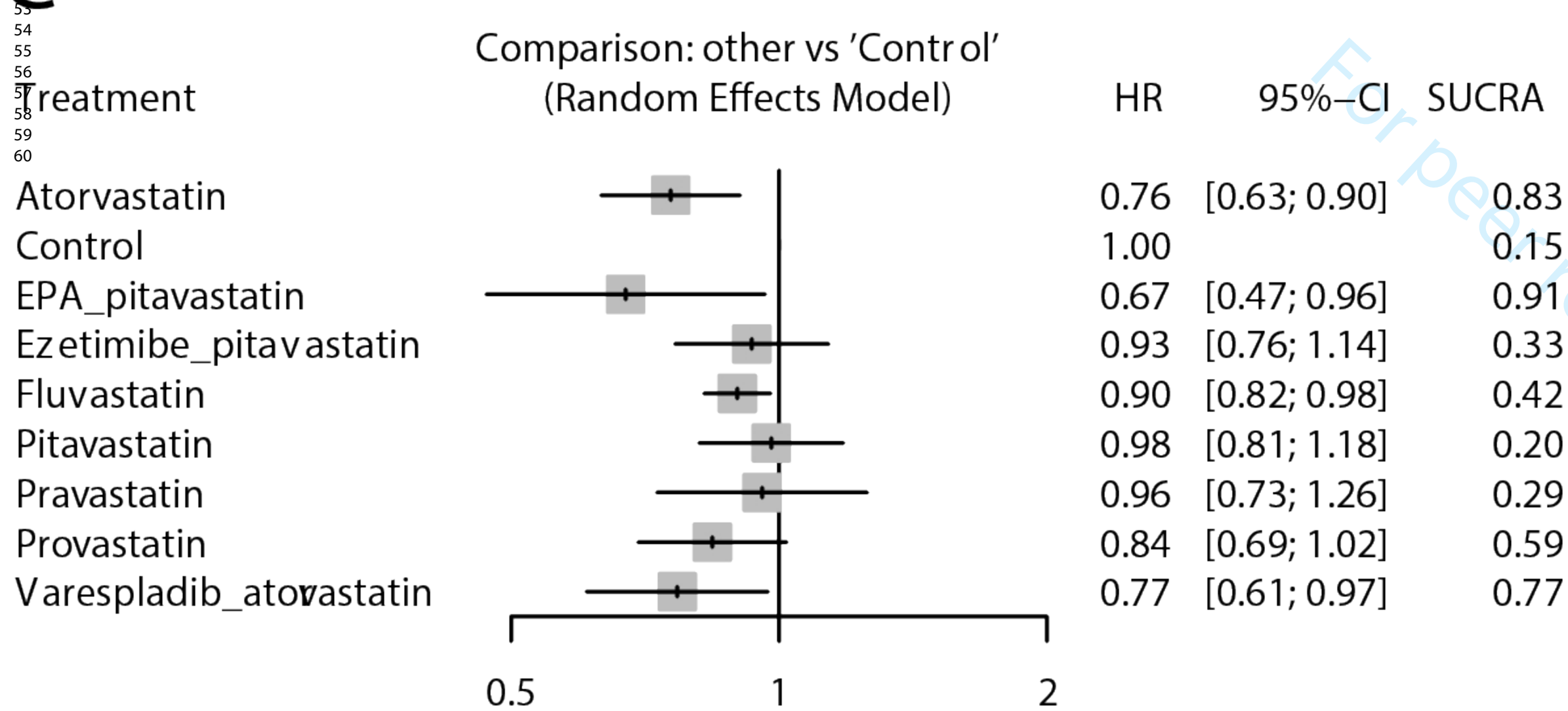
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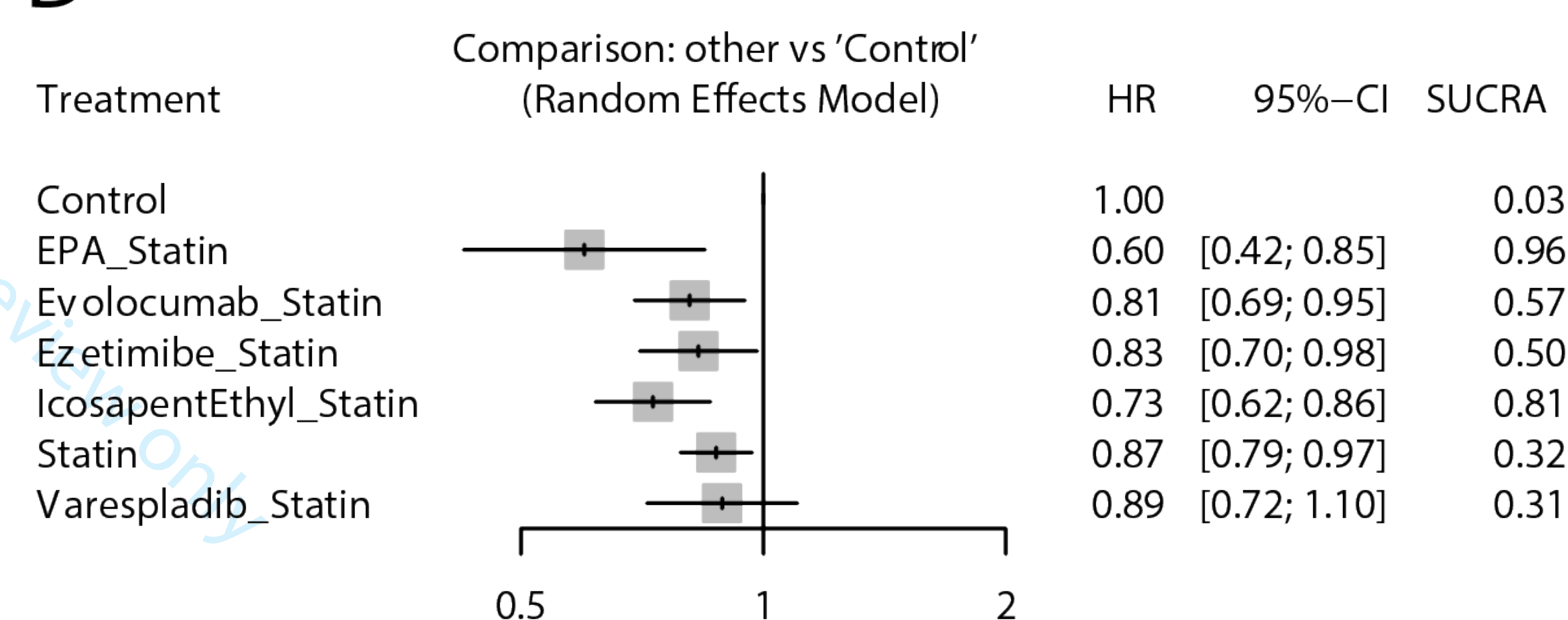
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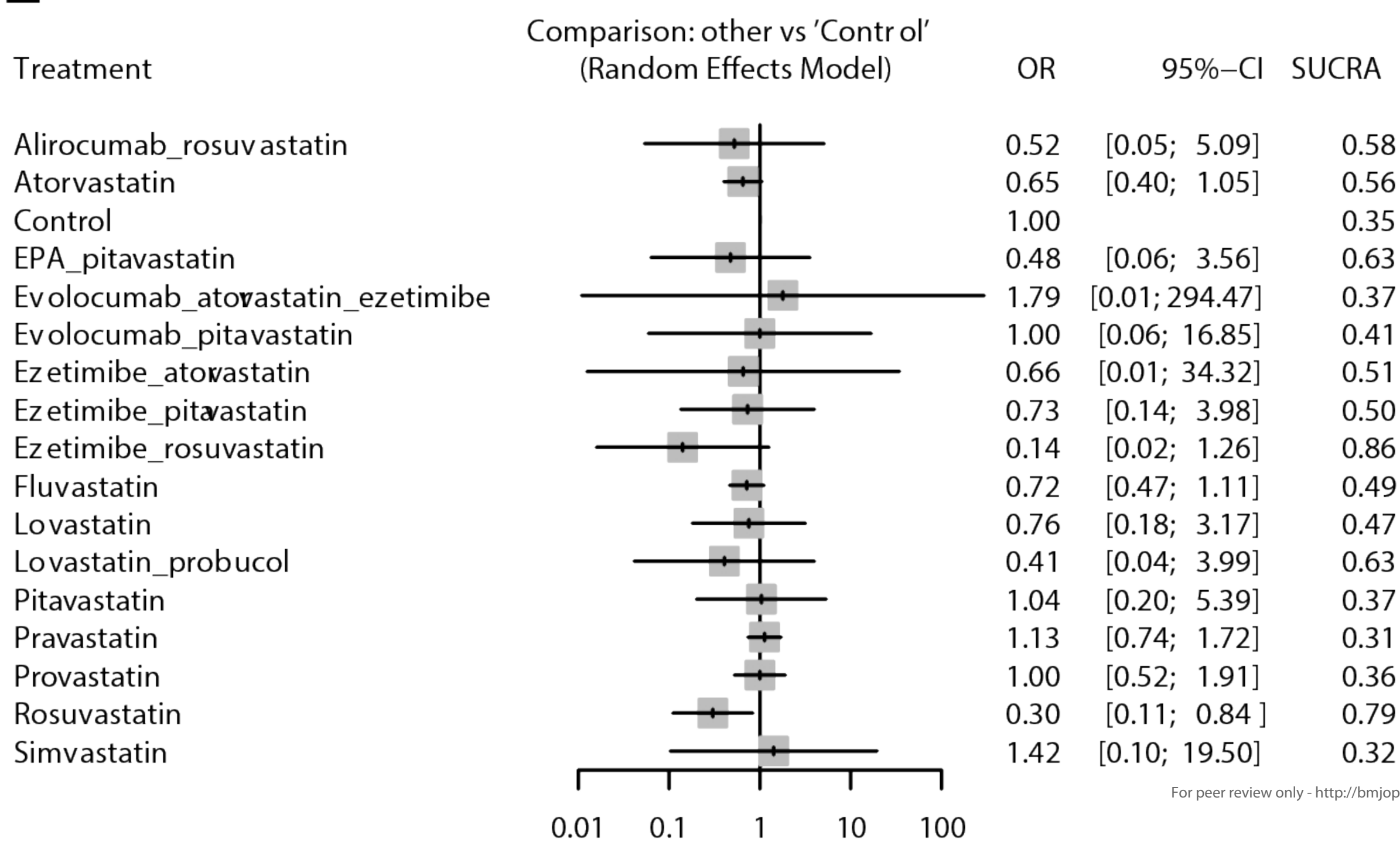
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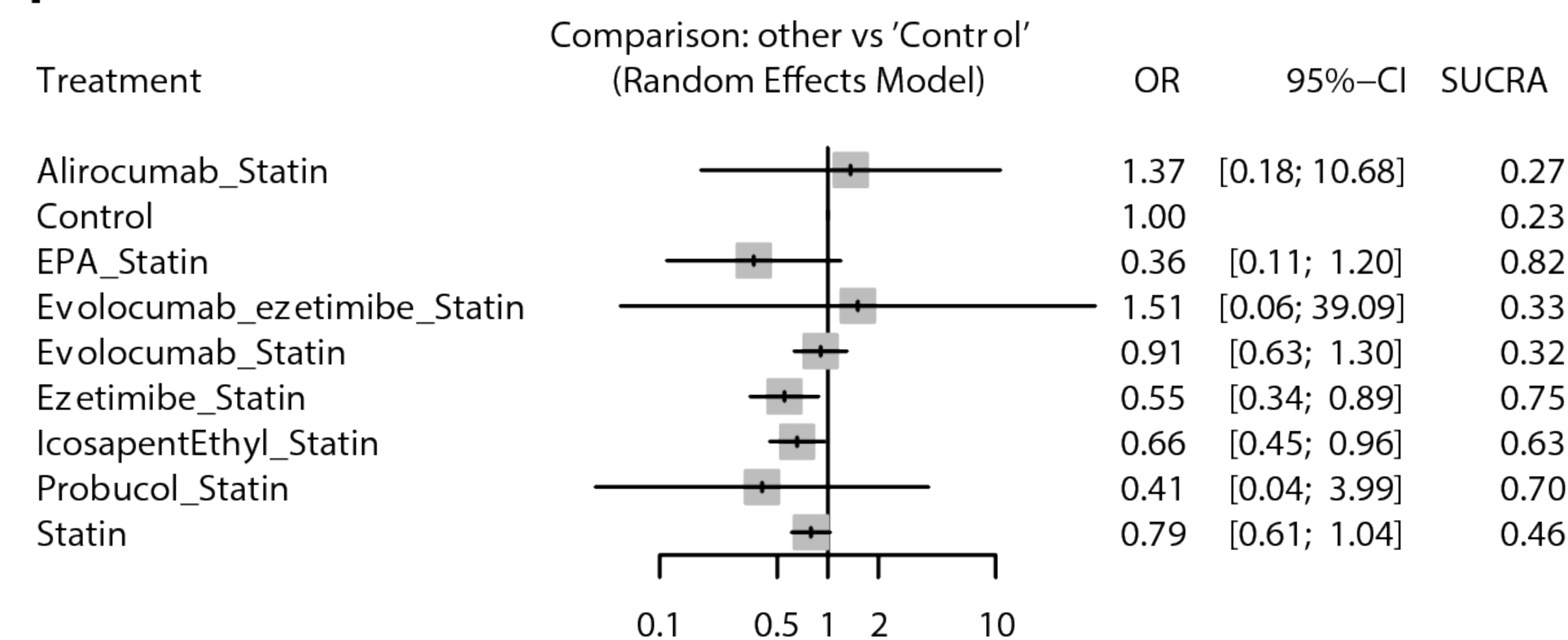
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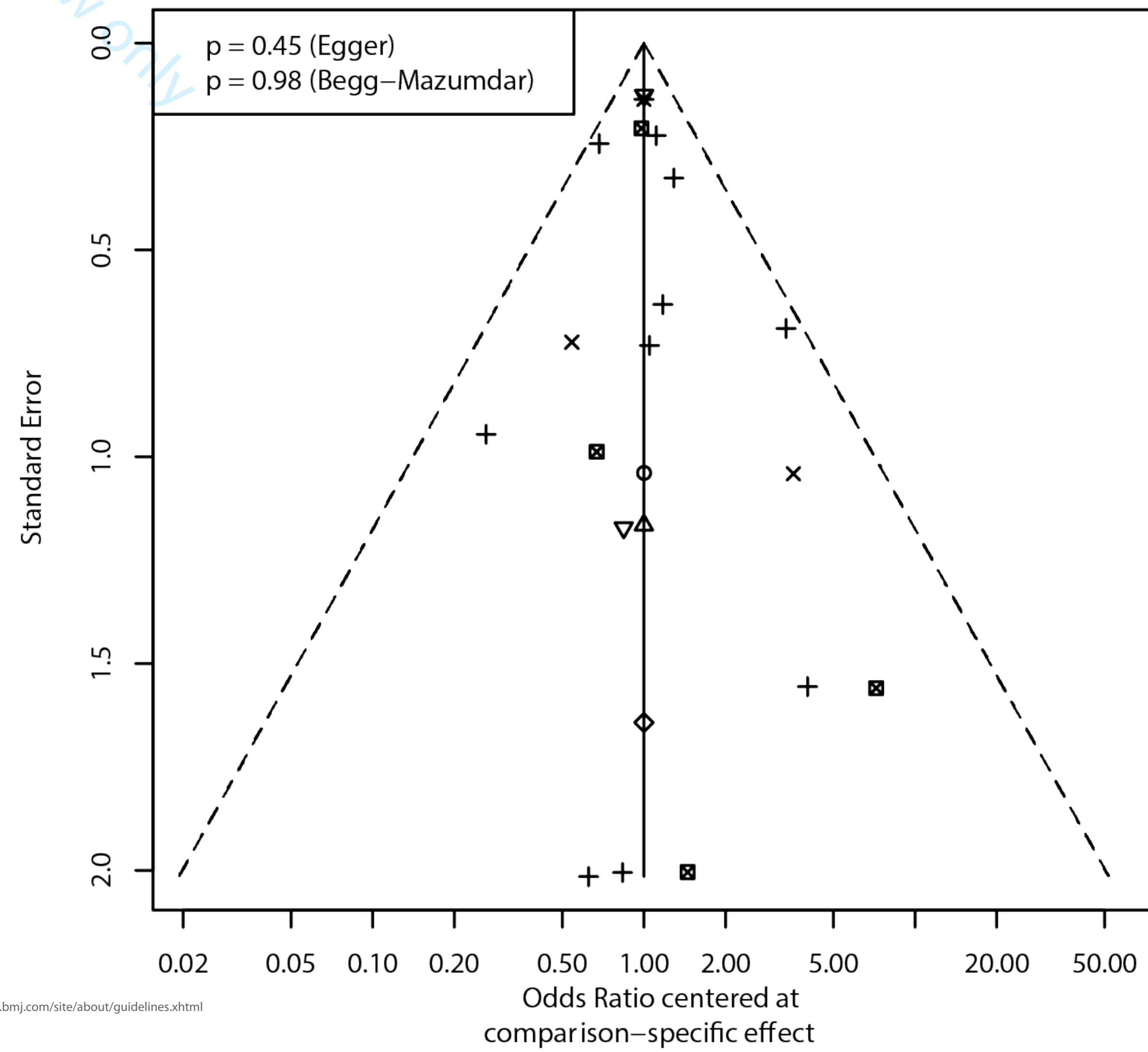
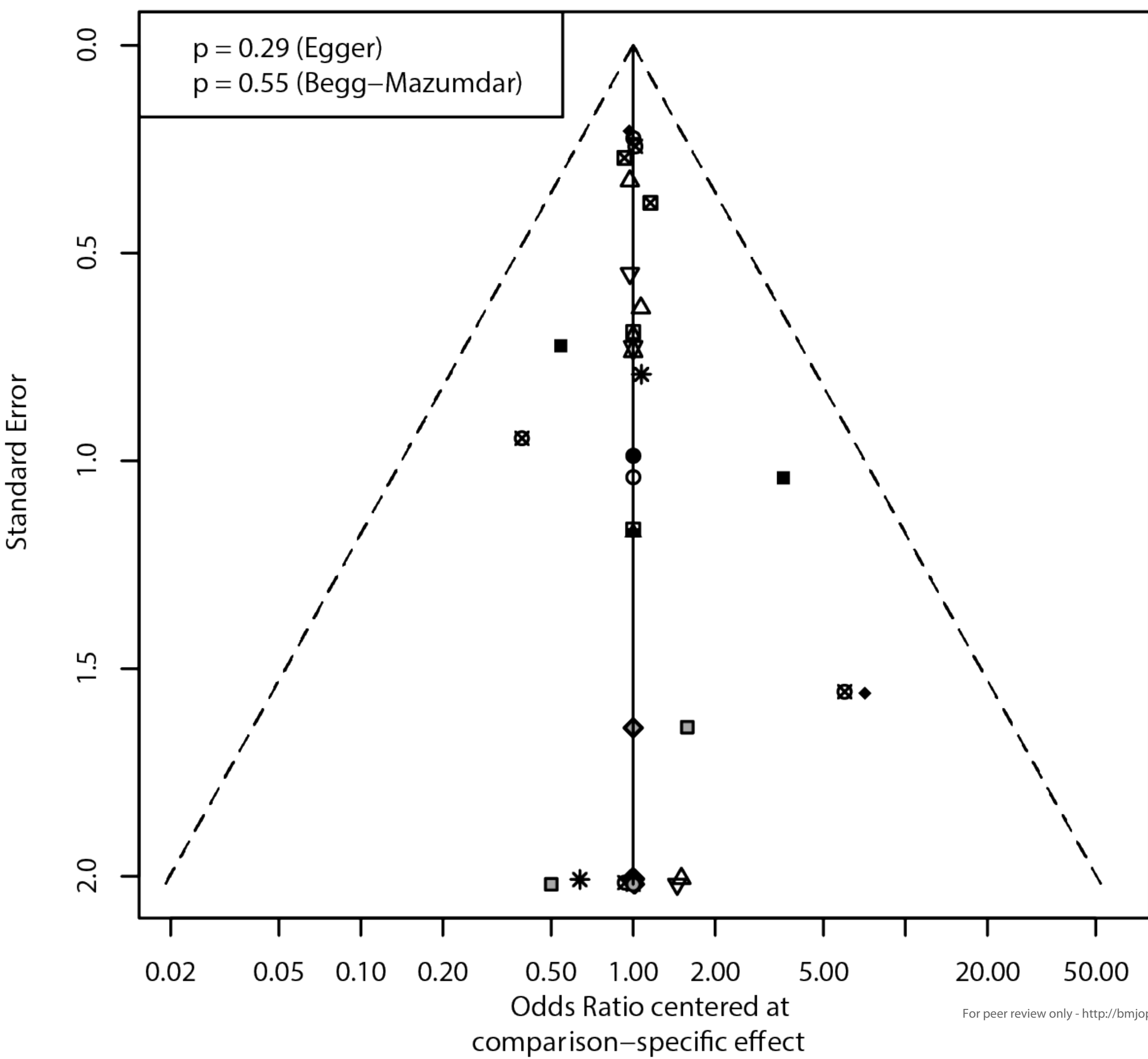
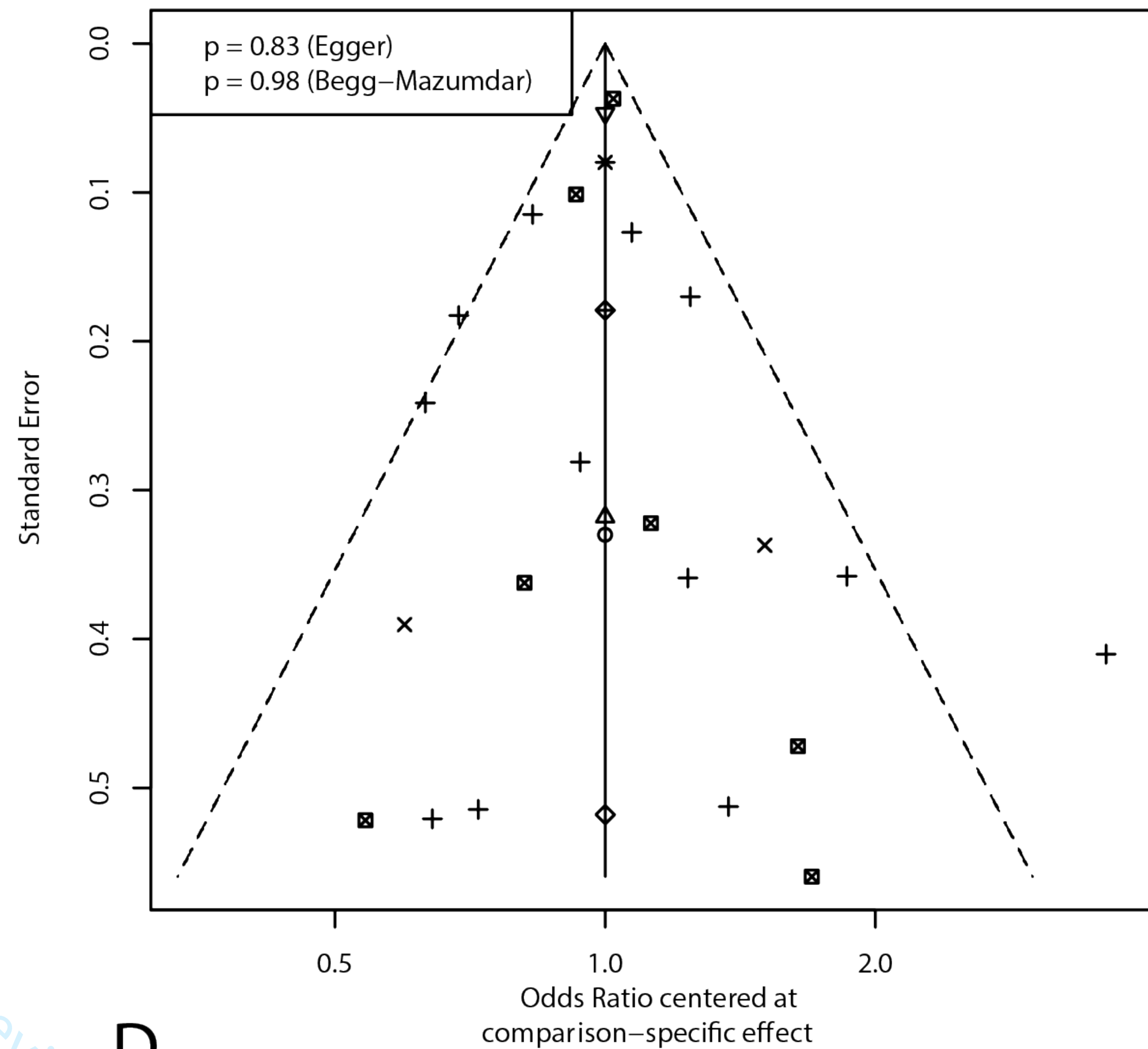
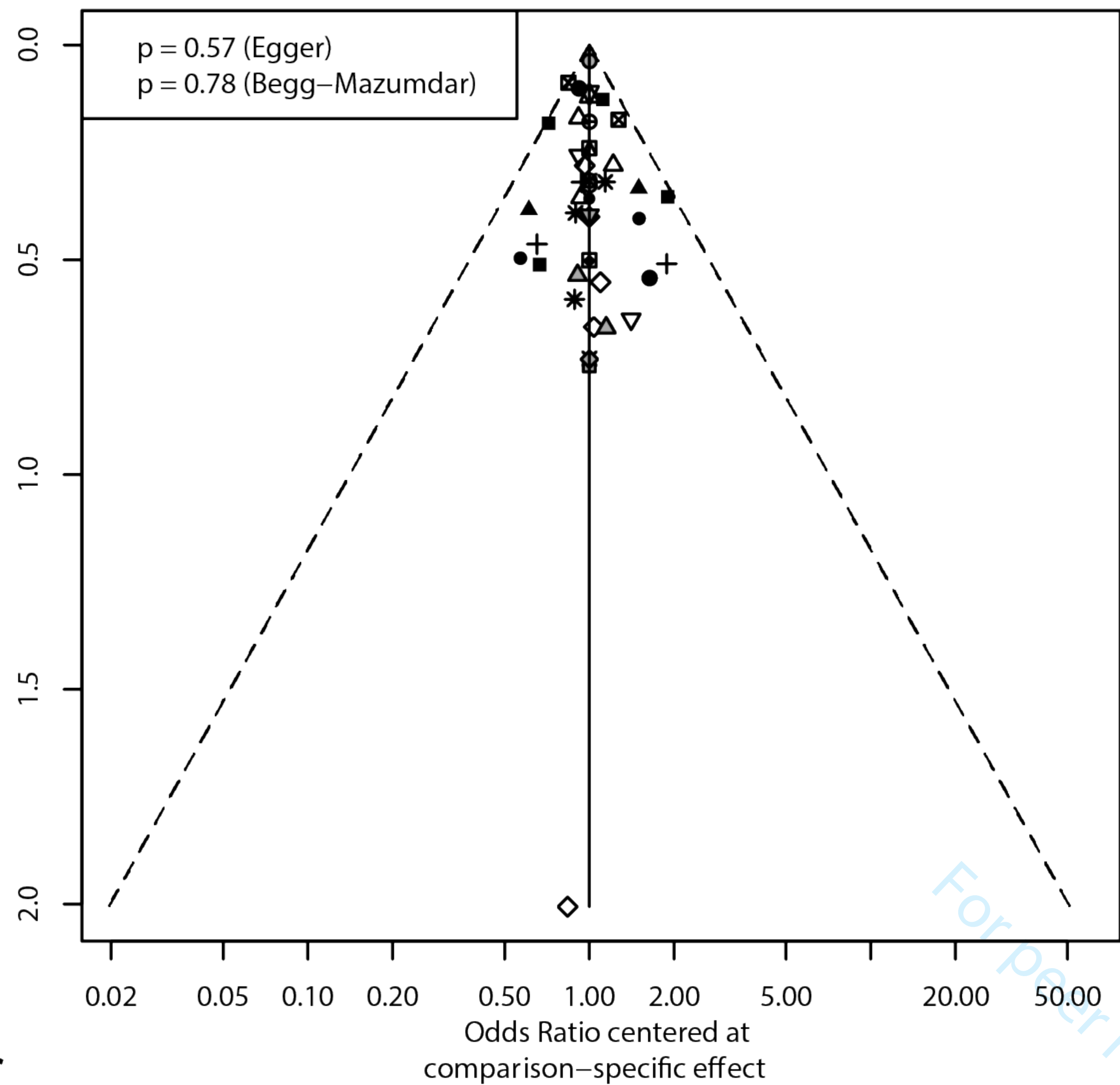
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PRISMA 2020 Checklist

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

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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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-070827.R2
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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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1 **Effectiveness of lipid-lowering therapy on mortality and**
2 **major adverse cardiovascular event outcomes in patients**
3 **undergoing percutaneous coronary intervention: a network**
4 **meta-analysis of randomized controlled trials**

5 Chang-Jiang Deng¹, Ju Yan², Ying-Ying Zheng¹, Ting-Ting Wu¹, Ying Pan¹, Xian-

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14 +8609914366168; Email: xiangxie999@sina.com

15 **Abstract**

16 **Background**

17 Emergency percutaneous coronary intervention (PCI) can quickly restore myocardial

18 perfusion after acute coronary syndrome (ACS). Whether and which lipid-lowering

19 regimens are effective in reducing major adverse cardiovascular events (MACEs) and

20 mortality risk after PCI remain unclear.

21

22 **Objective**

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

25 **Methods**

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

31 **Results**

32 Thirty-nine RCTs were included. For MACEs, alirocumab plus rosuvastatin (OR:
33 0.18; 95% CI: 0.07-0.44), evolocumab plus ezetimibe and statins (OR: 0.19; 95% CI:
34 0.06-0.59), eicosapentaenoic acid (EPA) plus pitavastatin (HR: 0.67; 95% CI: 0.49-
35 0.96), and icosapent ethyl plus statins (HR: 0.73; 95% CI: 0.62-0.86) had significant
36 advantages and relatively high rankings. For mortality, rosuvastatin (OR: 0.30; 95%
37 CI: 0.11-0.84), ezetimibe plus statins (OR: 0.55; 95% CI: 0.43-0.89) and icosapent
38 ethyl plus statins (OR: 0.66; 95% CI: 0.45-0.96) had significant advantages compared
39 to the control.

40 **Conclusion**

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

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4 43 reduce the risk of MACEs, but the risk of mortality remained unclear.
5

6 44 **Key words:** lipid-lowering therapy, major adverse cardiovascular events, mortality,
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9 45 network meta-analysis
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11 46 **Strengths and limitations of this study**

12 13 14 47 **The strengths of this study included the following:**

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17 48 only RCTs were considered for inclusion with high overall design quality;

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19 49 MACE and mortality were adopted as outcomes;

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22 50 the subjective factors of the investigator had little influence on the outcomes.
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24 25 51 **The limitations included the following:**

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27 52 this meta-analysis was based on the study level instead of the individual level;

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29 53 the criteria for defining MACEs varied among studies;

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32 54 many included studies only reported dichotomous outcomes but did not report the HR
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35 55 results.
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43 59 **Introduction**

44 60 Acute coronary syndrome (ACS) is a term used to refer to a range of conditions

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46 61 associated with acute myocardial ischaemia and/or infarction, which are usually due

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48 62 to coronary artery occlusion and acute ischaemic necrosis of the myocardium due to

49
50 63 progression of coronary atherosclerotic lesions(1, 2). Emergency percutaneous

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52 64 coronary intervention (PCI) can quickly restore myocardial perfusion(3). Although

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55 65 the development of technological and procedural PCI has resulted in substantial
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4 66 improvements in clinical outcomes, recurrent coronary events may still occur after
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6 67 PCI(4).
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9 68 The view of "residual cardiovascular risk" was introduced because MACEs still
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11 69 occurs in some patients who underwent PCI during follow-up. PCI can treat focal
12
13 70 manifestations of systemic progressive disease, but the residual risk of acute coronary
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15 71 syndrome is largely related to the systemic proatherosclerotic effect of poorly
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17 72 controlled cardiovascular risk factors(4). Lowering lipid levels, especially LDL-C,
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19 73 can halt the progression of coronary atherosclerosis and improve cardiovascular
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21 74 outcomes. Based on this view, it is believed that long-term optimal lipid-lowering
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23 75 therapy is effective in reducing long-term cardiovascular events after PCI. However,
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25 76 this view was still subject to challenges.
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35 78 Based on data from the "Korea Acute Myocardial Infarction Registry", the proponents
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37 79 concluded that patients treated with statins had significantly lower rates of MACEs,
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39 80 all-cause death, and cardiac death during the 2-year follow-up period after PCI
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41 81 application(5). However, a study of postoperative follow-up of PCI patients enrolled
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43 82 in the Melbourne Interventional Group registry concluded that statins have no
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45 83 significant beneficial effect on MACEs after PCI(6). The controversy may be
46
47 84 explained by two concepts: on the one hand, the optimal lipid reduction target may
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49 85 not be achieved by using single statins(7,8). On the other hand, long-term high-dose
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51 86 application of statins increases the risk of intracerebral haemorrhage and other side
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4 87 effects(9,10).
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9 89 There is a consensus on preloading high-dose statins to reduce MACEs in the
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11 90 perioperative period with PCI(11,12). However, there is still insufficient evidence for
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14 91 the continued application of lipid-lowering drugs to reduce the risk of long-term
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17 92 MACEs and mortality. This study assessed the benefits of different lipid-lowering
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19 93 regimens on the risk of MACEs and mortality in the post-PCI population by network
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22 94 meta-analysis.
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27 96 **Methods**

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30 97 This study was performed in accordance with the Preferred Reporting Items for
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32 98 Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study was
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35 99 registered with PROSPERO (CRD 42018099600).
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38 100 **Patient and Public Involvement**

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40 101 None
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45 103 **Search strategy**

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48 104 Public literature databases, including PubMed, Embase, and the Cochrane Library,
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50 105 were searched from inception to August 2022 without language restrictions using the
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53 106 following search terms: (lipid-lowering or statin or simvastatin or rosuvastatin or
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56 107 atorvastatin or fluvastatin or lovastatin or pravastatin or pitavastatin or mevastatin or
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4 108 ezetimibe or “eicosapentaenoic acid” or “icosapent ethyl” or “bempedoic acid” or
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6 109 fibrate or bezafibrate or gemfibrozil or fenofibrate or ciprofibrate or evolocumab or
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9 110 alirocumab or evinacumab or volanesorsen or vupanorsen or pelacarsen or olezarsen
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12 111 or inclisiran or olpasiran) and (“percutaneous coronary intervention” or “coronary
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14 112 angioplasty”) and (random* or randomized or randomized). The details of the full
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17 113 search strategy are listed in the Supplementary file. The references of relevant
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19
20 114 systematic reviews and meta-analyses were also searched to avoid omissions. The two
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23 115 authors conducted literature retrieval independently, and any conflicts were resolved
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25 116 through discussion with the third author.
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30 118 **Inclusion and exclusion criteria**

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32 119 The literature was included if it met the following criteria: 1) the study adopted a
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35 120 randomized controlled study design; 2) the study included patients who underwent
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38 121 PCI surgery or reported the subgroup of the population that underwent PCI; 3) the
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41 122 lipid-lowering regimen was applied to the population of the intervention group; 4) the
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44 123 control group used a different lipid-lowering agent or regimen; and 5) the study
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47 124 reported the outcome of mortality and/or MACEs. The exclusion criteria were as
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51 125 follows: 1) as preloading of statins before PCI was shown to have clear benefits, to
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54 126 determine whether application of lipid-lowering drugs after PCI also had beneficial
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57 127 effects, this work excluded studies on the preloading application of lipid-lowering
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60 128 drugs before PCI; and 2) although high-dose lipid-lowering agents, such as statins,

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4 129 have a better lipid-lowering effect, long-term application may bring potential side
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6 130 effects(9,13). Therefore, only studies in which all agents were considered to be
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9 131 applied at reasonable doses were included, and dose–response studies were excluded.
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12 132 In addition, repeatedly published studies, protocols, conference abstracts, reviews,
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14 133 comments and editorials were also excluded.

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19 135 Data extraction and quality assessment

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22 136 Two authors independently extracted the information from the included studies. The
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24 137 contents include the name of the first author, publication year, study location, sample
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27 138 size (population that underwent PCI), study abbreviation and registration number,
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30 139 lipid-lowering intervention and control, and follow-up time.

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35 141 The outcomes analysed were the incidence of all-cause mortality and MACEs,
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37 142 whether reported as dichotomous or hazard ratio (HR) statistics based on Cox
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40 143 regression. The MACE outcome was selected to most closely approximate the
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43 144 composite endpoint, including mortality, MI, stroke, coronary revascularization, and
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46 145 restenosis. Study quality was assessed by two investigators using the Cochrane risk of
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49 146 bias assessment tool, which included random sequence generation, allocation
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51 147 concealment, blinding of participants and personnel, blinding of outcome assessment,
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53 148 incomplete outcome data, selective reporting, and other potential biases.

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4 150 Statistical analysis
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6 151 We conducted frequentist network meta-analysis (NMA) using random-effects
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9 152 models weighted by the inverse variance method. Odds ratios (ORs) and 95%
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11 153 confidence intervals (CIs) were used for dichotomous outcomes. The hazard ratios
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14 154 (HRs) and 95% CIs based on Cox regression results were also pooled for reporting. If
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17 155 the HR value was not reported but there was a Kaplan–Meier survival curve, the HR
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19 156 value was extracted from the curve by GetData Graph Digitizer software version 2.24.
20
21
22 157 In network plots, the direct comparisons among treatment arms are shown, the end of
23
24 158 each line indicates a treatment arm, and the thickness of the lines indicates the number
25
26
27 159 of studies comparing the two treatments. Forest plots were used to describe the
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30 160 network comparison results between each treatment and the control.
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32 161 The restricted maximum likelihood estimation was used to quantify network
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35 162 heterogeneity. The Q statistic was used to assess the sum of statistics for
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38 163 heterogeneity (within designs) and for overall inconsistency (between designs)(14).
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41 164 The ranking probabilities of each regimen were estimated using the surface under the
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43 165 cumulative ranking curve (SUCRA), which was the ratio of the area under the curve
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46 166 to the entire area. A comparison-adjusted funnel plot was used to examine potential
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48 167 publication biases in the NMA. P values of less than 0.05 were considered to indicate
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51 168 statistical significance. The NMA was performed using R language with the
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54 169 “netmeta” package.
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171 Results

172 After removing duplicates, we obtained 1588 literature items. After screening the
 173 titles and abstracts, 1515 irrelevant studies were excluded. Seventy-three articles were
 174 screened for full text. The following articles were excluded: dose–response studies
 175 (8); those where no PCI population or subgroup was reported (6); those where no
 176 mortality or MACE-related outcomes were reported (6); repeated publications (5);
 177 studies related to preloading of lipid-lowering agents (4); studies unrelated to lipid-
 178 lowering agents (3); a protocol study (1); and a study with a non-RCT design (1).
 179 Finally, 39 articles were included, containing 54478 post-PCI patients (15-53) (Figure
 180 1).

181 **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. Pravastatin vs. Pitavastatin 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	Pravastatin	2Y
Han Yaling 2009 [41]	China	1275	-	NCT00405717	Atorvastatin	Pravastatin	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]	Netherlands	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

182 Abbreviations: EPA: eicosapentaenoic acid.

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4 183 #: Follow-up period: Y: years; M: months; W: weeks; D: days
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6 184 Among the included studies, the publication period ranged from 1991 to 2022. The
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9 185 research locations were mainly in Asia (China, Japan and South Korea), Europe
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11 186 (Netherlands, France, and Italy), America, and multiple centres. There were 10 studies
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14 187 with sample sizes greater than 1000 patients. There were also 22 studies with publicly
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17 188 available clinical study registration numbers (Table 1). In terms of design quality, all
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19 189 included studies were RCTs. Therefore, the design quality was generally high. The
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21
22 190 main factors potentially affecting design quality were the blinding of participants and
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24 191 personnel and blinding of outcome assessment (Figure 2). However, as the desired
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27 192 outcomes were mortality and MACEs, the subjective factors of the investigator had
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29
30 193 little influence on the outcomes.
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32 194 As two studies did not specify the types of statins, the network meta-analysis was
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35 195 divided into two parts. One part was analysed based on specific types of statins, and
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38 196 the other was based on taking statins as a whole. For the dichotomous results of
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41 197 MACEs, the NMA based on specific types of statins included 18 lipid-lowering
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43 198 regimens. The Q test for heterogeneity ($p = 0.07$) and inconsistency ($p = 0.16$) were
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45
46 199 nonsignificant, indicating no evidence of heterogeneity or inconsistency in the NMA.
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48 200 In pairwise comparisons with the control, alirocumab plus rosuvastatin (OR: 0.18;
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51 201 95% CI: 0.07-0.44; SUCRA: 0.94), evolocumab plus atorvastatin and ezetimibe (OR:
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53 202 0.18; 95% CI: 0.05-0.63; SUCRA: 0.90), and ezetimibe plus rosuvastatin (OR: 0.29;
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56 203 95% CI: 0.11-0.76; SUCRA: 0.80) had significant advantages and relatively high
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4 204 SUCRA rankings. No potential publication bias was found according to the
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6 205 comparison-adjusted funnel plot (Figure 3).
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11 207 In the NMA based on taking statins as a whole, ten regimens were analysed.
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14 208 Evolocumab plus ezetimibe and statins (OR: 0.19; 95% CI: 0.06-0.59; SUCRA: 0.92),
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17 209 alirocumab plus statins (OR: 0.27; 95% CI: 0.13-0.59; SUCRA: 0.87), and icosapent
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20 210 ethyl plus statins (OR: 0.39; 95% CI: 0.25-0.62; SUCRA: 0.72) had significant
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22 211 advantages and relatively high SUCRA rankings. No potential publication bias was
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25 212 found.
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30 214 For the HR results of MACEs, the NMA based on specific types of statins included
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33 215 nine regimens. The Q test for heterogeneity was nonsignificant ($p = 0.964$) because
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36 216 the network comparisons lacked loops. Therefore, the results were considered
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39 217 consistent. Compared to the control, eicosapentaenoic acid (EPA) plus pitavastatin
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42 218 (HR: 0.67; 95% CI: 0.49-0.96; SUCRA: 0.91), atorvastatin (HR: 0.76; 95% CI: 0.63-
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45 219 0.90; SUCRA: 0.83), and varespladib plus atorvastatin (HR: 0.77; 95% CI: 0.61-0.97;
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48 220 SUCRA: 0.77) had significant advantages and relatively high SUCRA rankings.

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51 221 Potential publication bias was not analysed due to the small number of included
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54 222 studies.
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57 224 In the NMA based on taking statins as a whole, seven regimens were analysed. EPA
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4 225 plus statins (HR: 0.60; 95% CI: 0.42-0.85; SUCRA: 0.96) and icosapent ethyl plus
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6 226 statins (HR: 0.73; 95% CI: 0.62-0.86; SUCRA: 0.81) had significant advantages over
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9 227 the control.

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14 229 For the dichotomous mortality results, the NMA based on specific types of statins
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17 230 included 17 lipid-lowering regimens. The Q test for heterogeneity ($p = 0.78$) and
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19 231 inconsistency ($p = 0.99$) were nonsignificant. Due to the rare occurrence of events, the
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22 232 results of the comparison had low precision with a large standard error. Compared to
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25 233 the control, only rosuvastatin (OR: 0.30; 95% CI: 0.11-0.84; SUCRA: 0.79) showed a
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27 234 significantly better effect. Ezetimibe plus rosuvastatin had a relatively high SUCRA
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30 235 ranking, but there was no significant difference compared to the control (OR: 0.14;
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32 236 95% CI: 0.02-1.26; SUCRA: 0.86). No potential publication bias was found (Figure
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40 239 In the NMA based on taking statins as a whole, nine regimens were analysed.
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43 240 Ezetimibe plus statins (OR: 0.55; 95% CI: 0.43-0.89; SUCRA: 0.75) and icosapent
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45 241 ethyl plus statins (OR: 0.66; 95% CI: 0.45-0.96; SUCRA: 0.63) had significant
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48 242 advantages compared with the blank control group. No potential publication bias
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51 243 existed. NMA analysis was not performed due to the small number of studies
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53 244 reporting HRs for mortality (Figure 5).

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4 **246 Discussion**

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6 247 This study analysed the benefits of lipid-lowering therapy on mortality and MACE
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9 248 outcomes in patients who underwent PCI by network meta-analysis. The results
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11 249 showed that several lipid-lowering regimens could reduce the risk of MACEs
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14 250 compared with the blank control. Icosapent ethyl plus statins had the benefit of
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17 251 reducing both the risk of MACEs and mortality. However, EPA plus statins had more
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19 252 advantages in reducing the risk of MACEs. Of note, based on the current evidence,
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22 253 alirocumab and evolocumab plus statins had obvious advantages in reducing the risk
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25 254 of MACEs but had no obvious benefit in reducing the risk of mortality.

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30 256 EPA is a long-chain omega-3 polyunsaturated fatty acid. Long-term intake of EPA
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32 257 can reduce the residual cardiovascular risk to reduce the risk of MACEs(54). In terms
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35 258 of pathological mechanisms, EPA combined with pitavastatin was shown to reduce
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38 259 the lipid volume of coronary artery plaques and total atherosclerotic plaque volume in
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41 260 patients who underwent PCI, which may be the reason for the reduced risk of
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43 261 MACEs(55).

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48 263 Icosapent ethyl is a highly purified and stable eicosapentaenoic acid ethyl ester that
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51 264 has potential higher anti-inflammatory, antioxidant, plaque stability and cell
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53 265 membrane stability effects(56). In the NMA results, icosapent ethyl plus statins had
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56 266 significant benefits for reducing the risk of either mortality or MACEs in patients who

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4 267 underwent PCI, which was an ideal regimen for the population.
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9 269 Ezetimibe inhibits the absorption of cholesterol and has a synergistic lipid-lowering
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11 270 pharmacological effect with statins to further reduce the risk of death and MACEs. In
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13 271 particular, when combined with rosuvastatin, ezetimibe has a stronger lipid-lowering
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15 272 effect with a high safety profile without the risk of drug interactions(57). Our NMA
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17 273 results also showed that ezetimibe can reduce the risk of MACEs and mortality.
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22 274 According to the guidelines for the management of dyslipidaemia from the European
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24 275 Society of Cardiology and the European Atherosclerosis Society, ezetimibe was
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26 276 recommended if the LDL-C target was not reached(58,59). The American College of
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28 277 Cardiology guidelines also recommend adding ezetimibe when using maximally
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30 278 tolerated statin therapy and if LDL-C levels remained ≥ 70 mg/dL(60). These benefits
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32 279 have also been demonstrated in the secondary prevention of PCI.
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40 281 Alirocumab and evolocumab are both proprotein convertase subtilisin/kexin type-9
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42 282 inhibitors (PCSK9is), which can increase the level of LDL receptor in the liver, thus
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44 283 improving the ability of the liver to bind LDL-C and reducing the level of peripheral
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46 284 LDL-C(61). There was also a synergistic lipid-lowering pharmacological effect when
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48 285 PCSK9is were combined with statins that resulted in a significantly reduced LDL-C
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50 286 concentration and atherosclerosis event risk; however, there was still controversy
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52 287 regarding the mortality risk reduction(62). It has been suggested that the powerful
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4 288 effect of PCSK9is on reducing LDL-C predisposes patients to hypocholesterolaemia,
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7 289 which will not increase the risk of cerebral haemorrhage. PCSK9is may be the
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9 290 preferred lipid-lowering agents in patients with elevated ICH risk (63-65). On the
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11 291 other hand, PCSK9is did not reduce serum inflammatory factors in one study,
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14 292 suggesting that they may not reduce the risk of residual inflammation in the post-PCI
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17 293 population(66).

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22 295 In the results of this study, lipid-lowering therapy strategies had general advantages in
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24 296 reducing MACE risk. However, for all-cause mortality, the advantage of lipid-
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27 297 lowering therapy was not obvious. Based on dichotomous outcomes of mortality,
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30 298 some strategies may even have a tendency to increase the mortality risk. This
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33 299 challenges the opinion that lipid-lowering therapy is recommended after PCI(67). A
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35 300 large sample size retrospective study suggests that statins can reduce the risk of all-
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38 301 cause death in patients with coronary artery disease undergoing PCI, regardless of
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41 302 individual cholesterol levels(68). Alternatively, the “lipid paradox” view has been
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44 303 proposed and indicates that higher levels of LDL-C and triglycerides on admission are
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47 304 associated with better clinical outcomes. Especially in patients with ST-elevation
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50 305 myocardial infarction, lower LDL-C levels were associated with worse mortality
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53 306 outcomes(69). However, this view is also controversial(70).

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56 308 On the other hand, it is possible that the contribution of LDL-C reduction to the risk

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4 309 of mortality outcomes is obscured by other confounding factors. For example,
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6 310 inflammatory status may also have had an important impact on patient mortality risk.
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9 311 In a cohort of post-PCI patients with low LDL-C levels, residual inflammatory risk
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11 312 also had a significant effect on overall mortality(71). C-reactive protein can also
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13 313 predict long-term mortality in post-PCI patients independent of LDL-C levels(72). In
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15 314 addition, cardiac remodelling also has an important impact on the survival outcome of
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17 315 post-PCI patients(73).
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19 316 There are several limitations in this study. First, this analysis was based on the study
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21 317 level instead of the individual level, making it difficult to consider the individual
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23 318 confounding factors in the analysis. Second, two included studies did not specify the
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25 319 type of statins, so our study had to be analysed separately according to whether all
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27 320 statins were considered as a whole. Third, the criteria for defining MACEs varied
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29 321 among studies, which contributed to heterogeneity among the study results. Fourth,
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31 322 many included studies only reported dichotomous outcomes but did not report the HR
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33 323 results, resulting in missing relevant data for the analysis.
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326 In conclusion, the results of this study suggested that EPA, especially icosapent ethyl,
327 plus statins had a beneficial effect on reducing the risk of MACEs and mortality in
328 post-PCI patients. PCSK9is plus statins were able to reduce the risk of MACEs, but
329 the effects on the risk of mortality remained unclear.

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336

337 **Author contributions**

338 Chang-Jiang Deng completed the manuscript, Ju Yan, Ting-Ting Wu, Ying Pan, Ying-

339 Ying Zheng guided the data analysis and the production of the figures, Xian-Geng

340 Hou, Si-Fan Wang, Subinur Sirajidin, Mikereyi Aimaitijiang, Xiang Xie read and

341 approved the final manuscript.

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346 **Availability of data and materials**

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

349

350 **Declarations**

351

352 **Ethics approval and consent to participate**

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

354

355 **Consent for publication**

356 not applicable.

357

358 **Competing interests**

359 The authors declare that they have no competing interests.

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46 672 **Figure 1.** Flowchart of the study selection process for eligible studies
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48 673 **Figure 2.** Methodological quality assessment of included studies
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51 674 **Figure 3.** Network plots of comparisons for major outcomes included in the analyses.
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53 675 A: dichotomous results of MACE based on specific types of statins; B: dichotomous
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56 676 results of MACE based on taking statins as a whole; C: hazard ratio results of MACE
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4 677 based on specific types of statins; D: hazard ratio results of MACE based on taking
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6 678 statins as a whole; E: dichotomous results of mortality based on specific types of
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9 679 statins; F: dichotomous results of mortality based on taking statins as a whole.
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11 680 **Figure 4.** Forest plots of lipid-lowering therapy compare to control for outcomes in
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14 681 network meta-analysis with SUCRA ranking results. A: dichotomous results of
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16 682 MACE based on specific types of statins; B: dichotomous results of MACE based on
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18 683 taking statins as a whole; C: hazard ratio results of MACE based on specific types of
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20 684 statins; D: hazard ratio results of MACE based on taking statins as a whole; E:
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22 685 dichotomous results of mortality based on specific types of statins; F: dichotomous
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24 686 results of mortality based on taking statins as a whole.

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29 687 **Figure 5.** The comparison-adjusted funnel plot for assessing all main outcomes. A:
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31 688 dichotomous results of MACE based on specific types of statins; B: dichotomous
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33 689 results of MACE based on taking statins as a whole; C: dichotomous results of
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35 690 mortality based on specific types of statins; D: dichotomous results of mortality based
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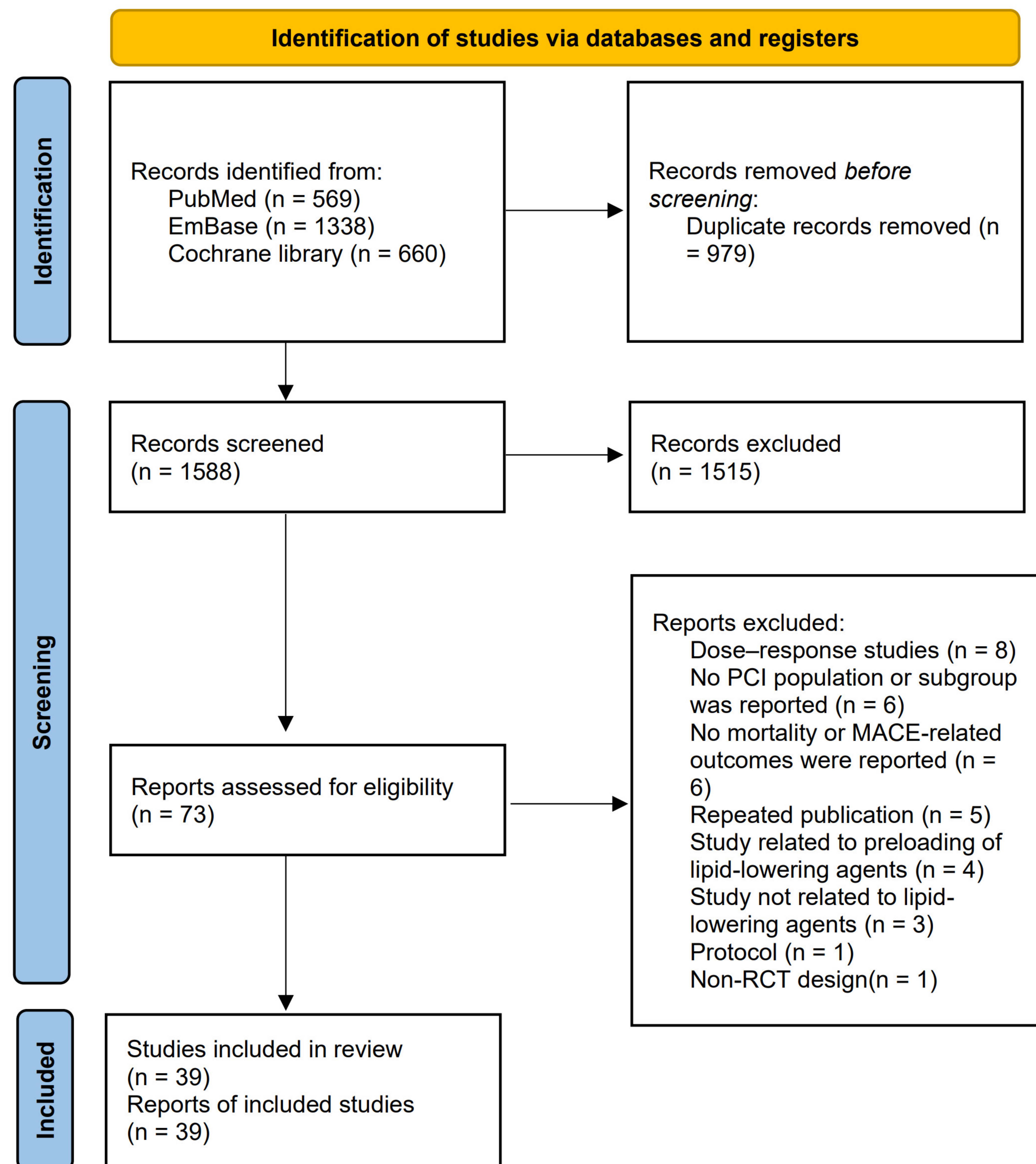
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22 705 **Authors and Afliations**
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PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



*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).

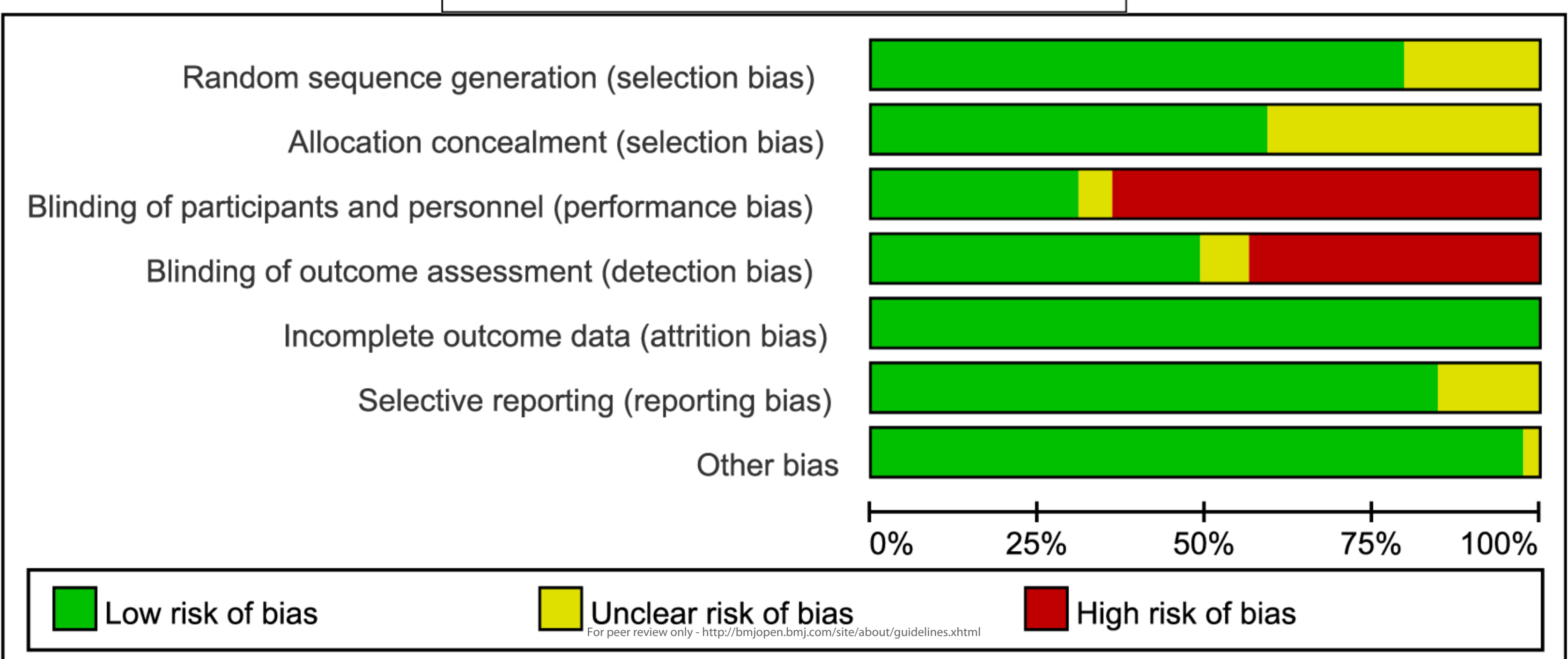
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

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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	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	+	?	-	-	+	+	?

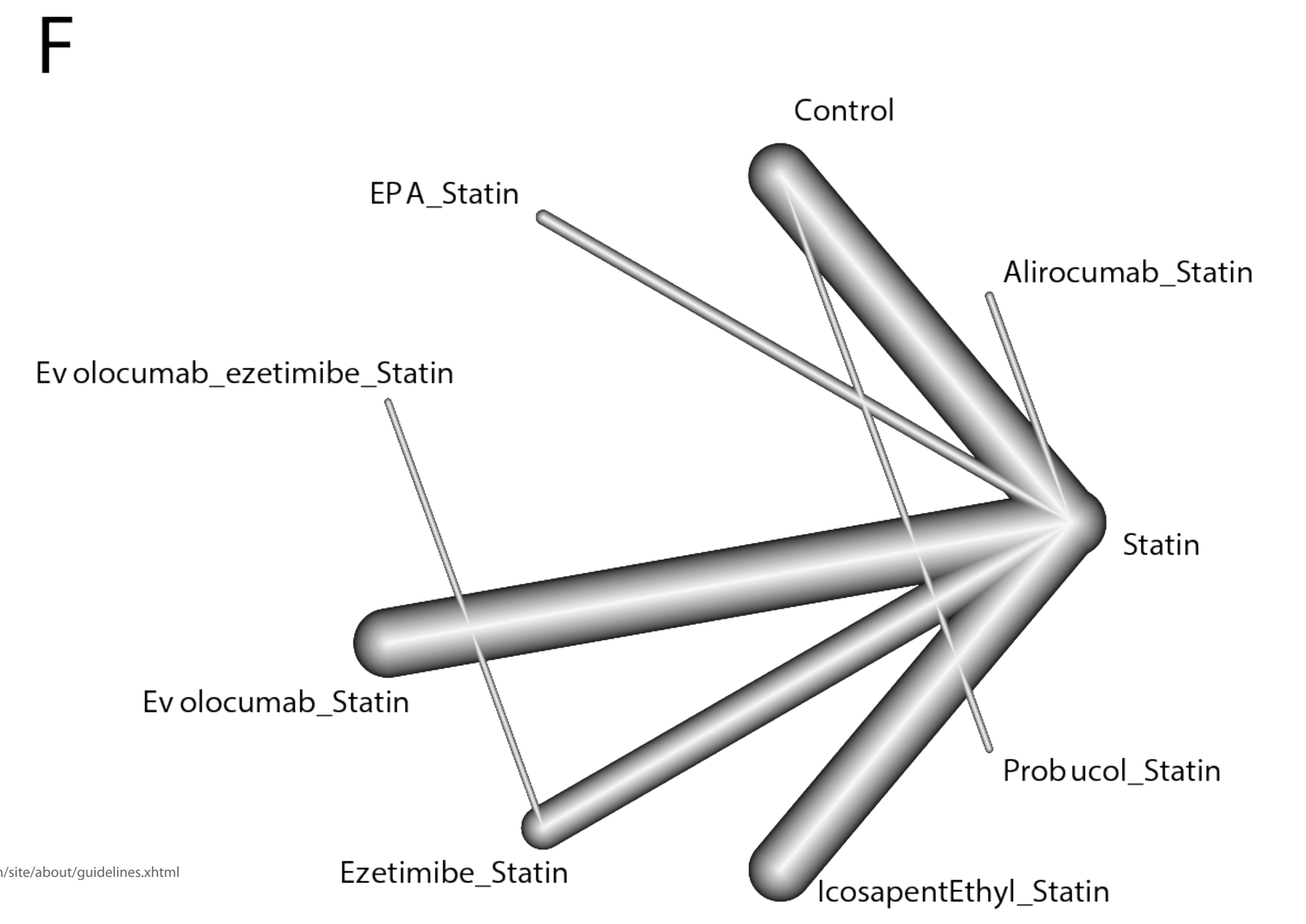
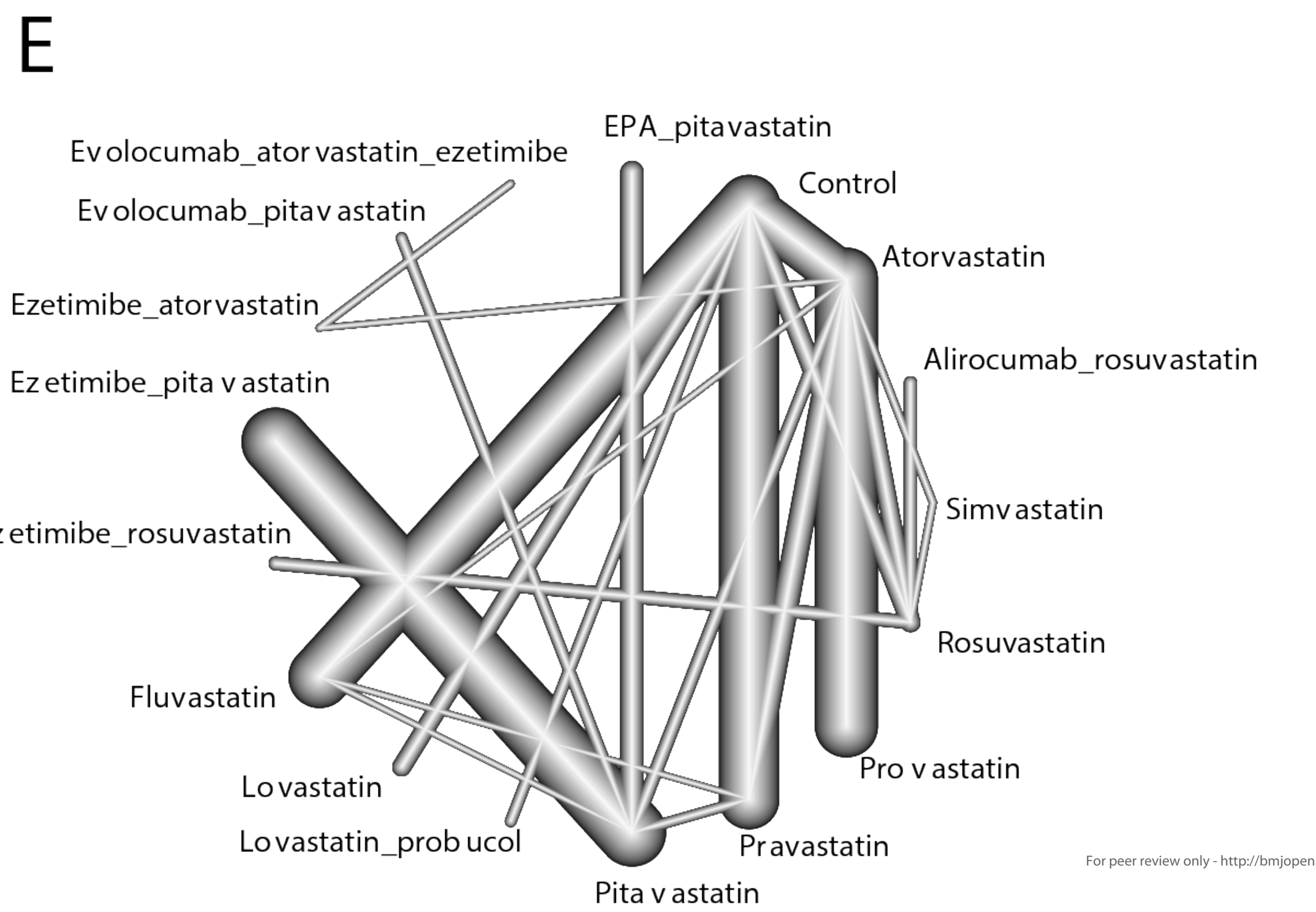
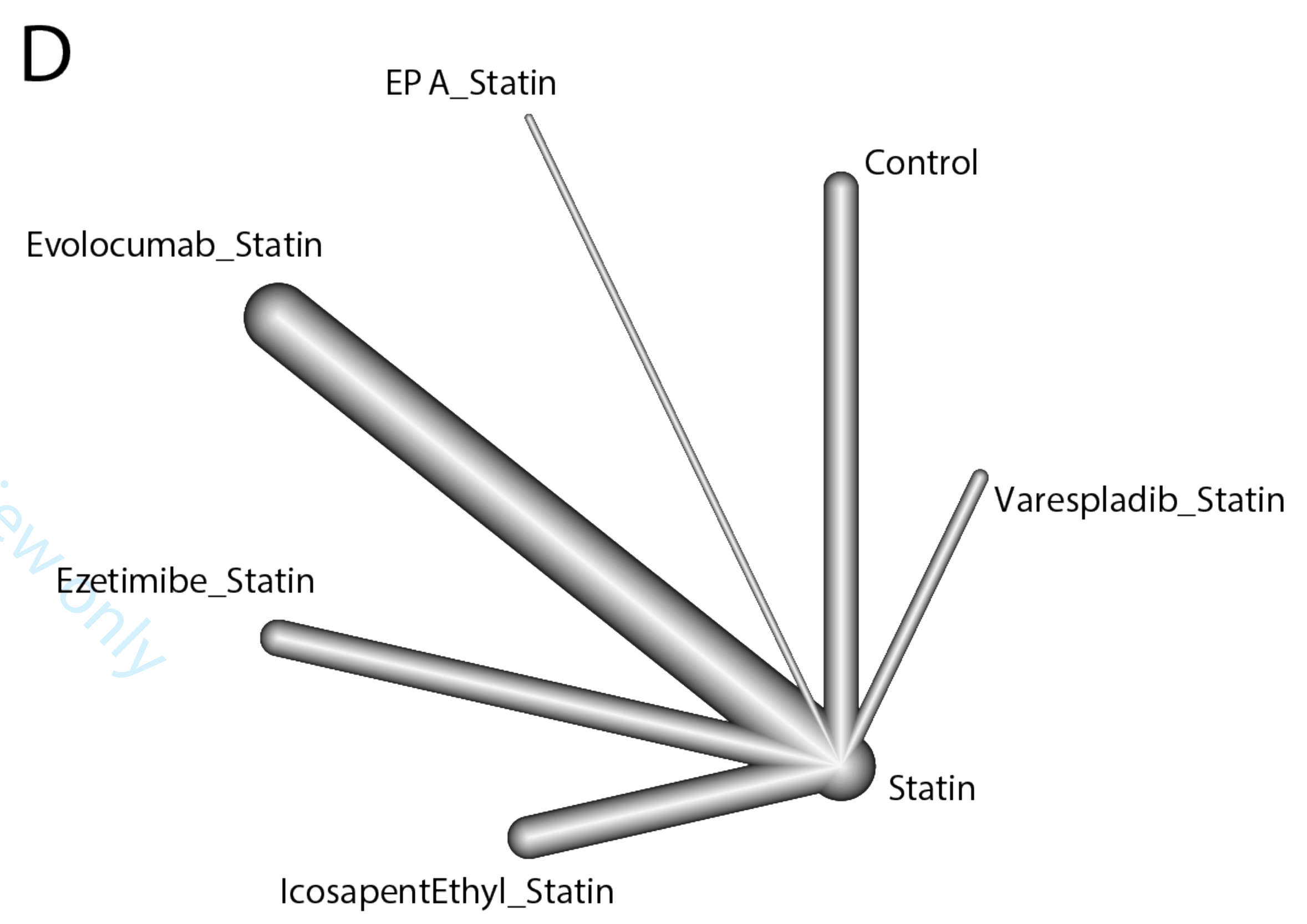
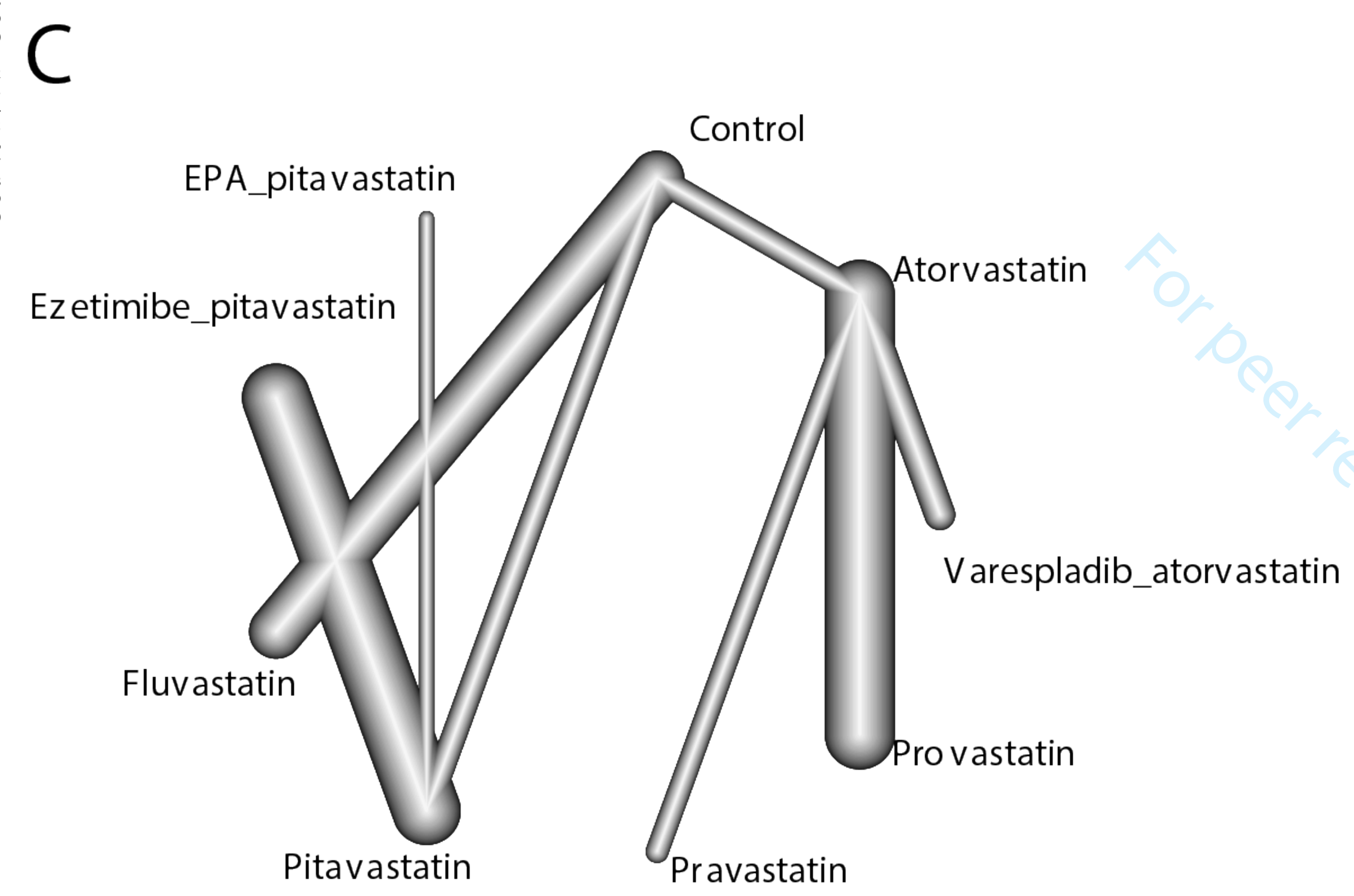
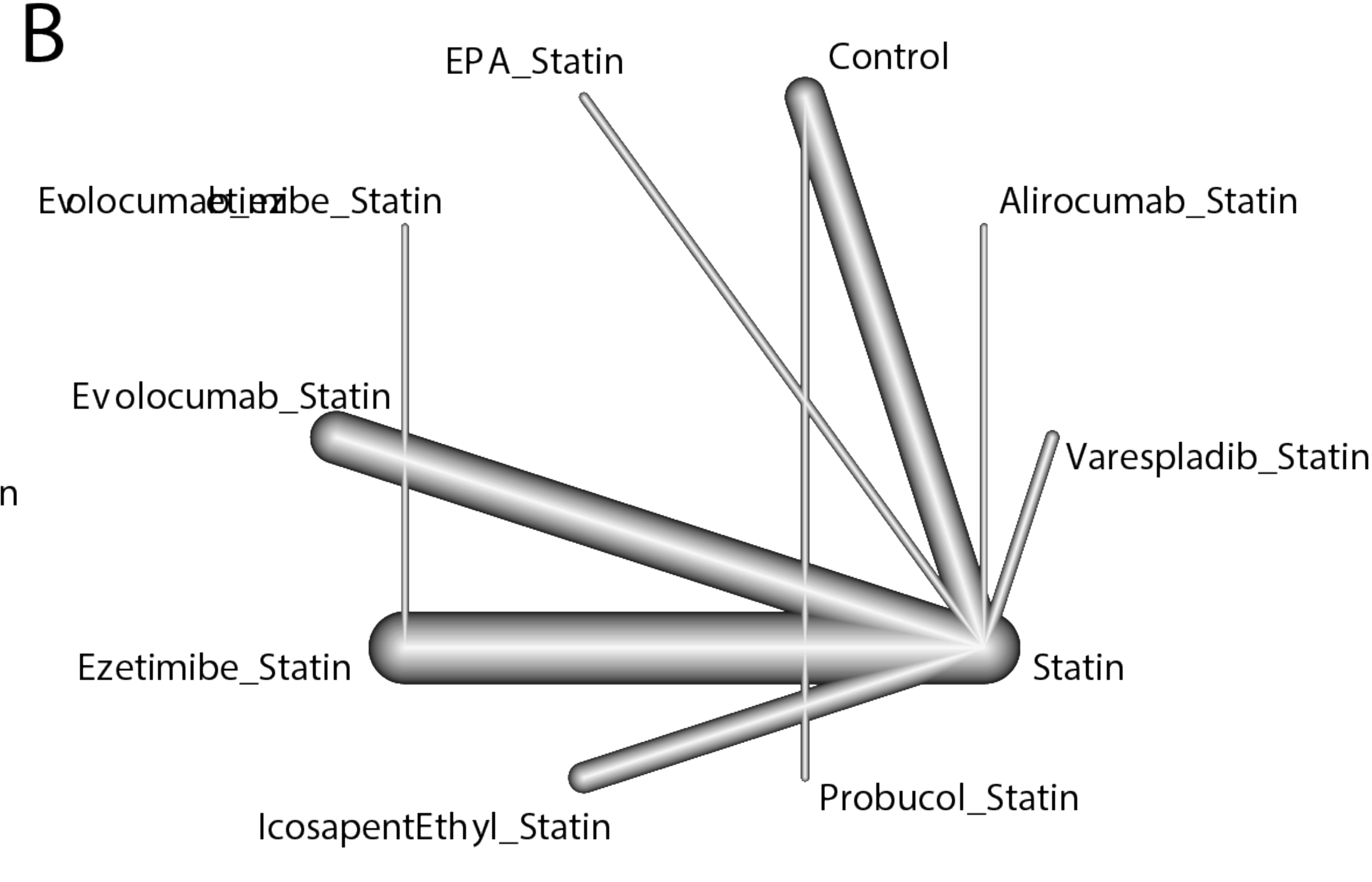
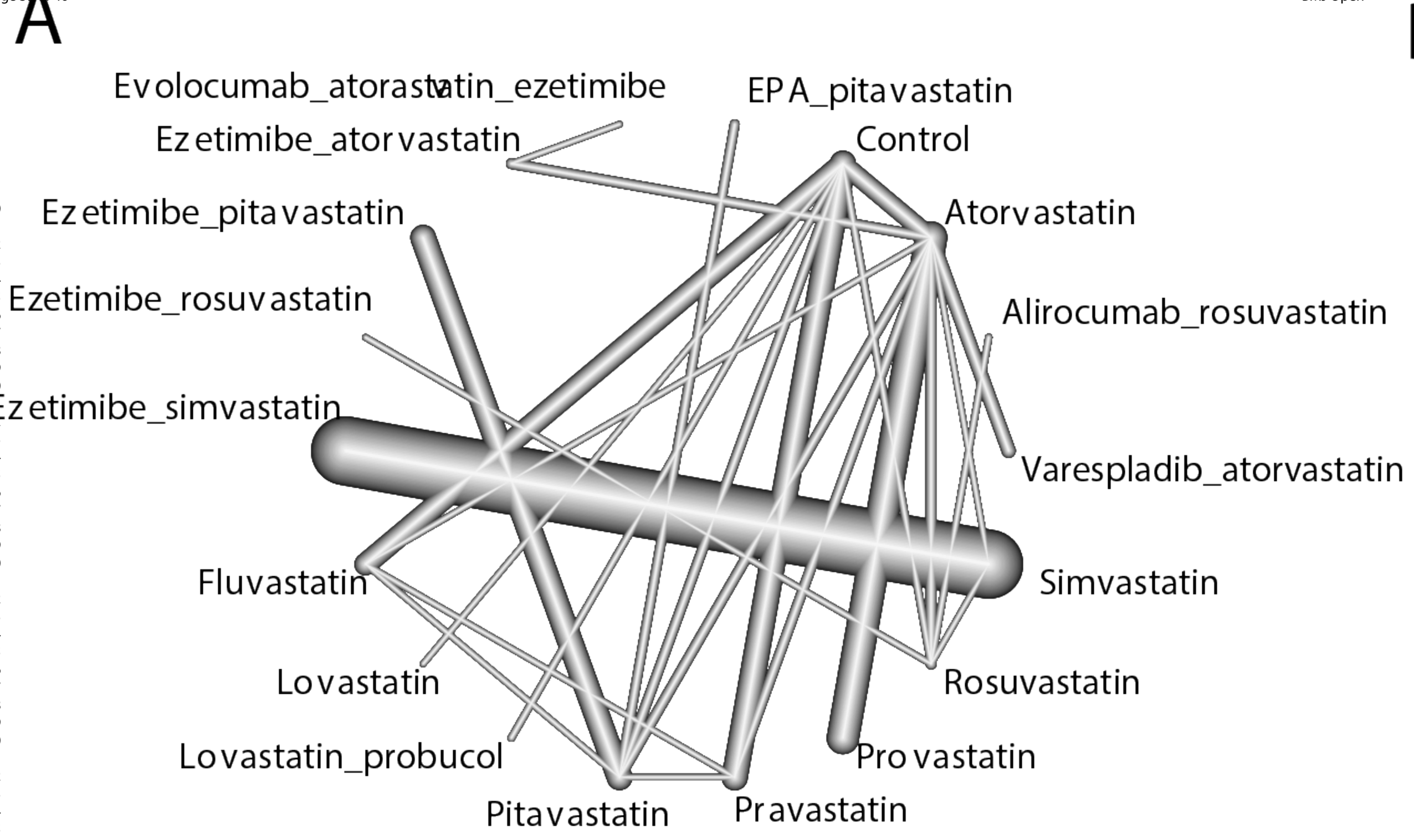


Low risk of bias

Unclear risk of bias

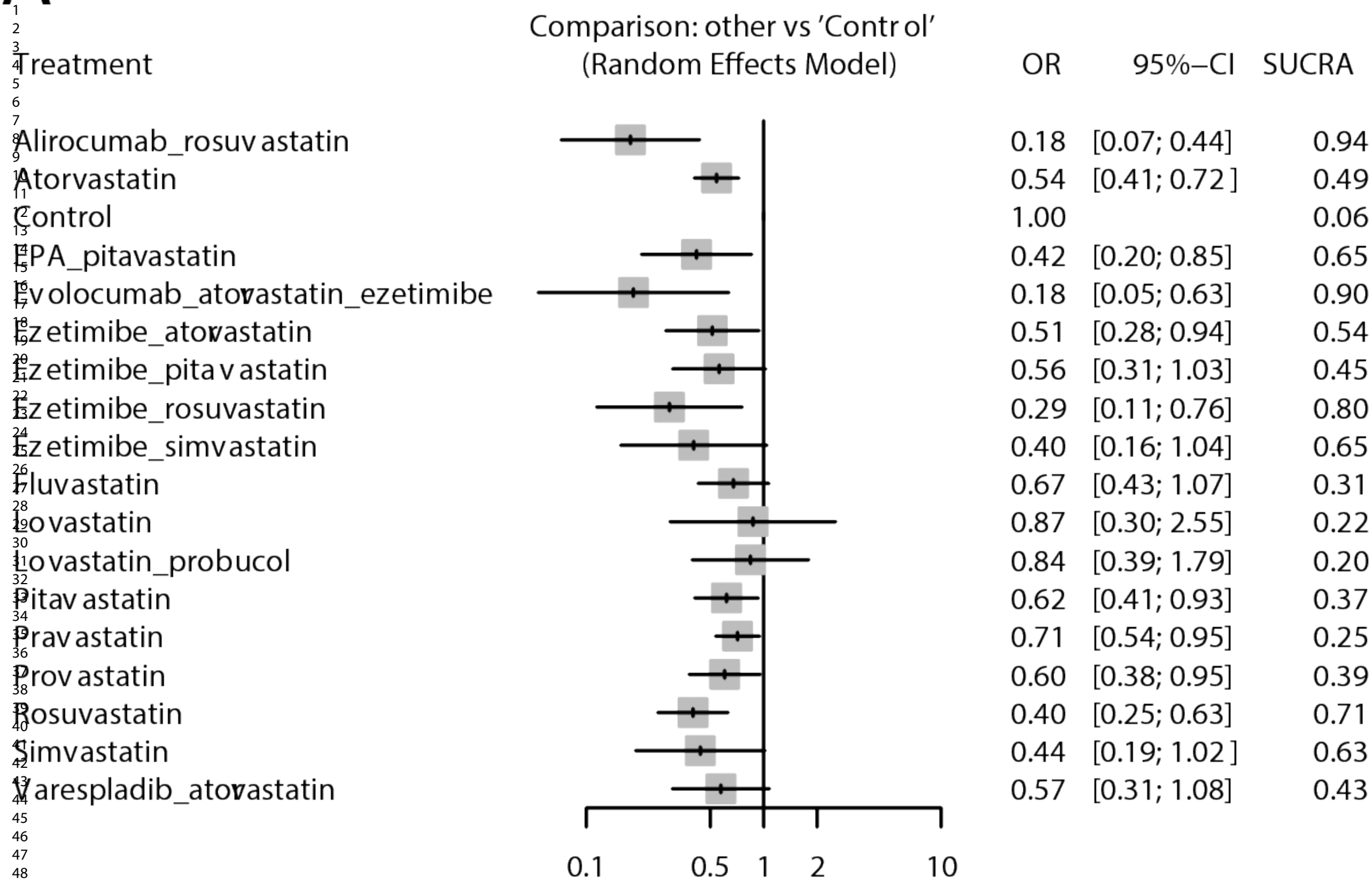
High risk of bias

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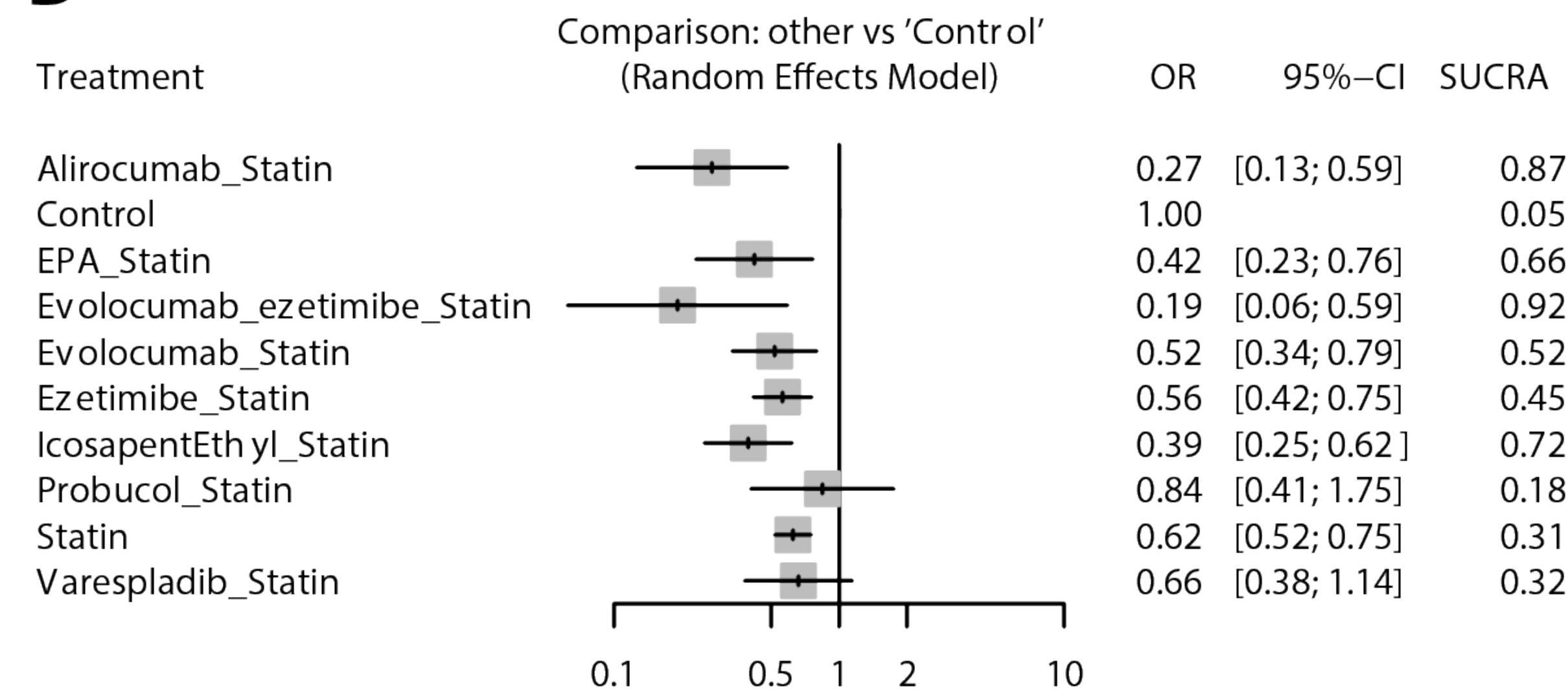


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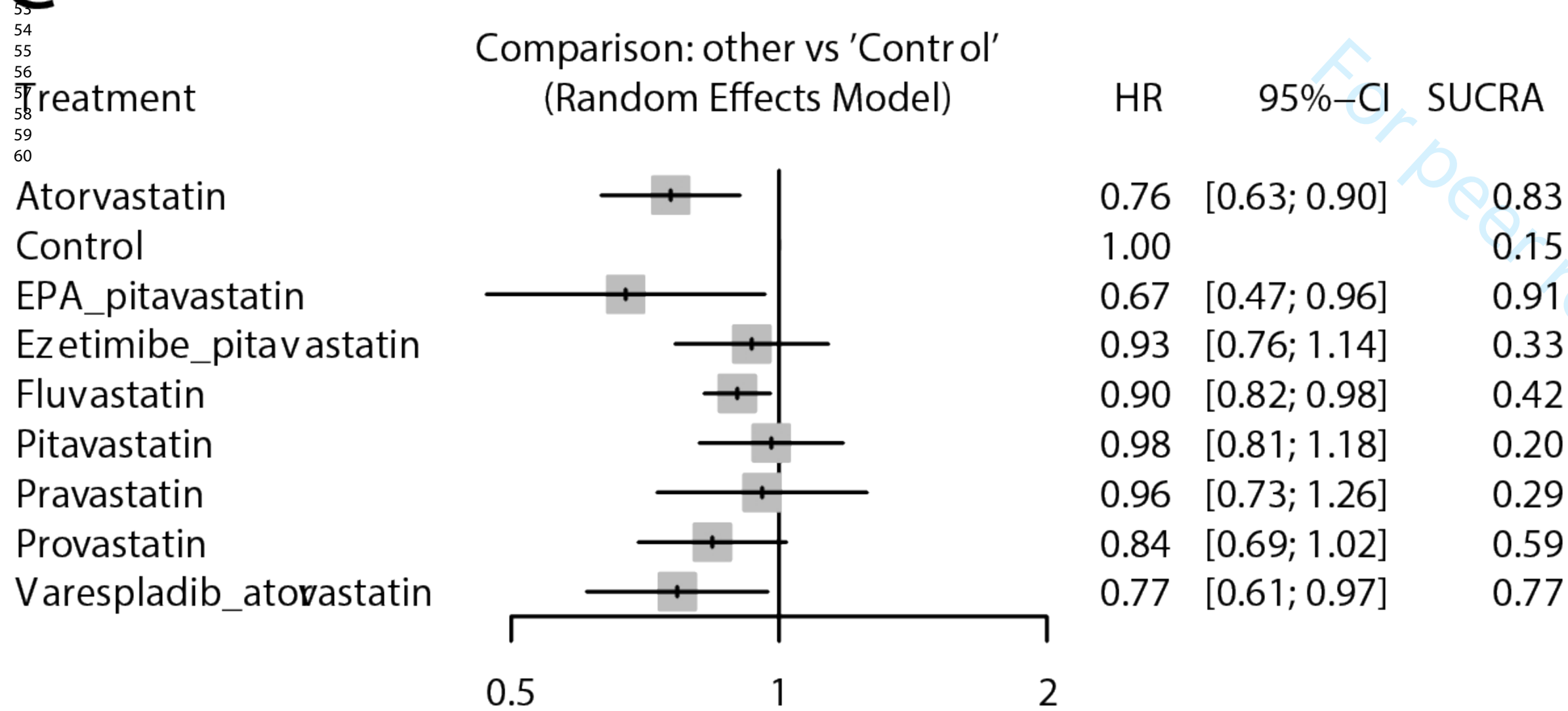
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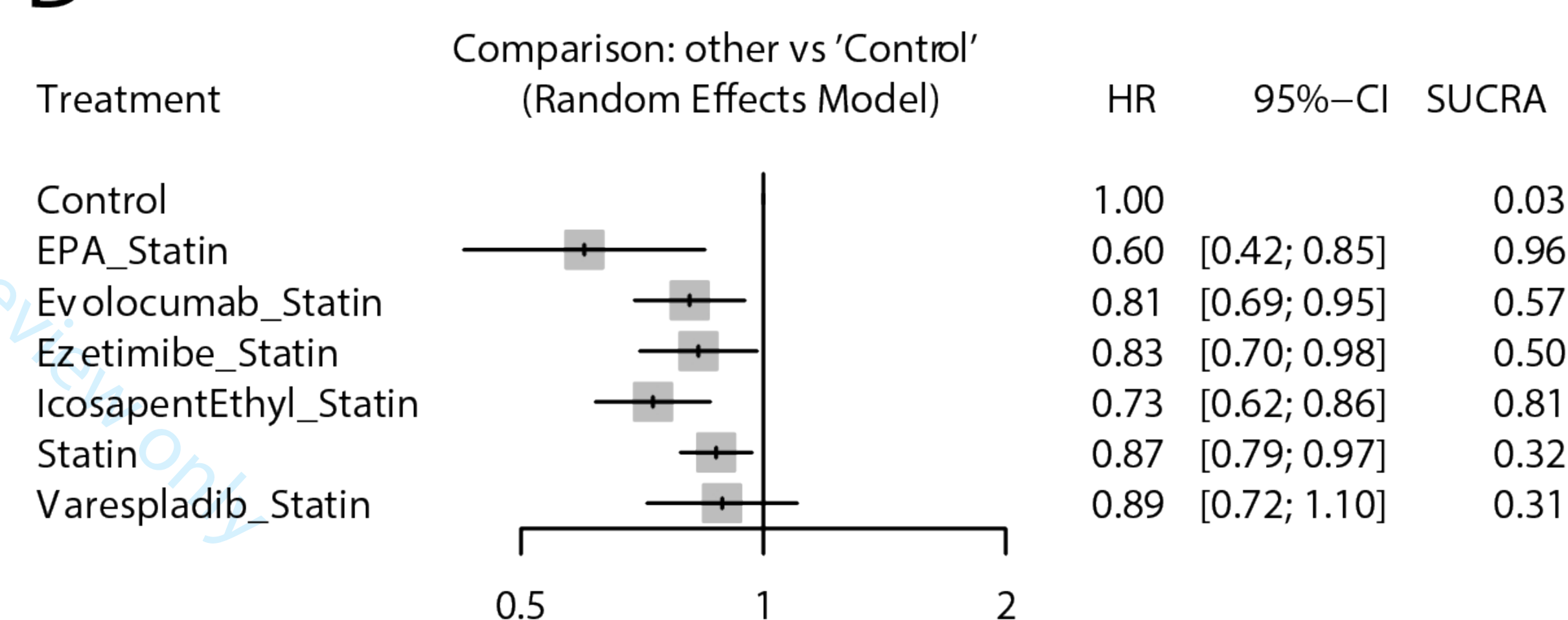
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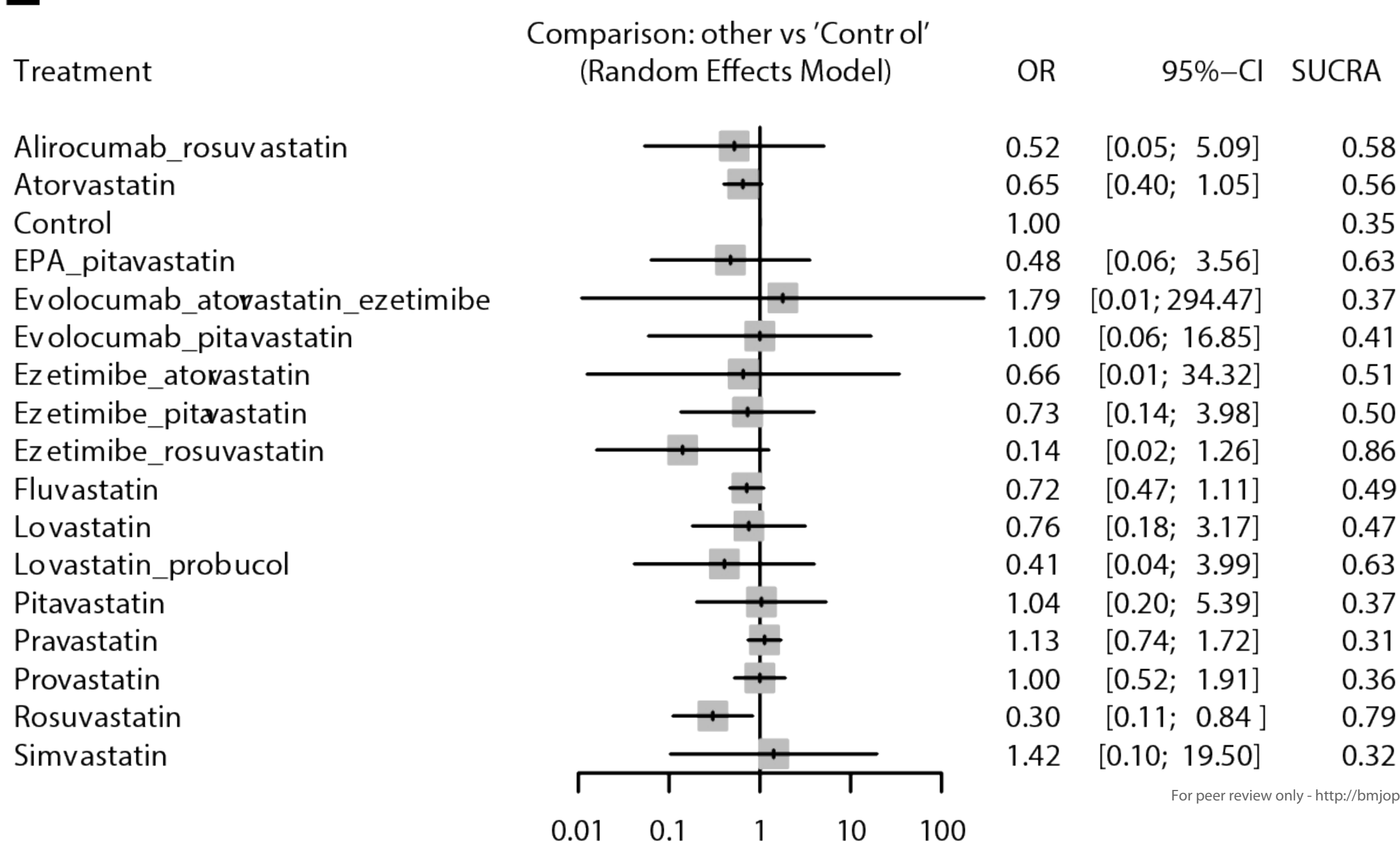
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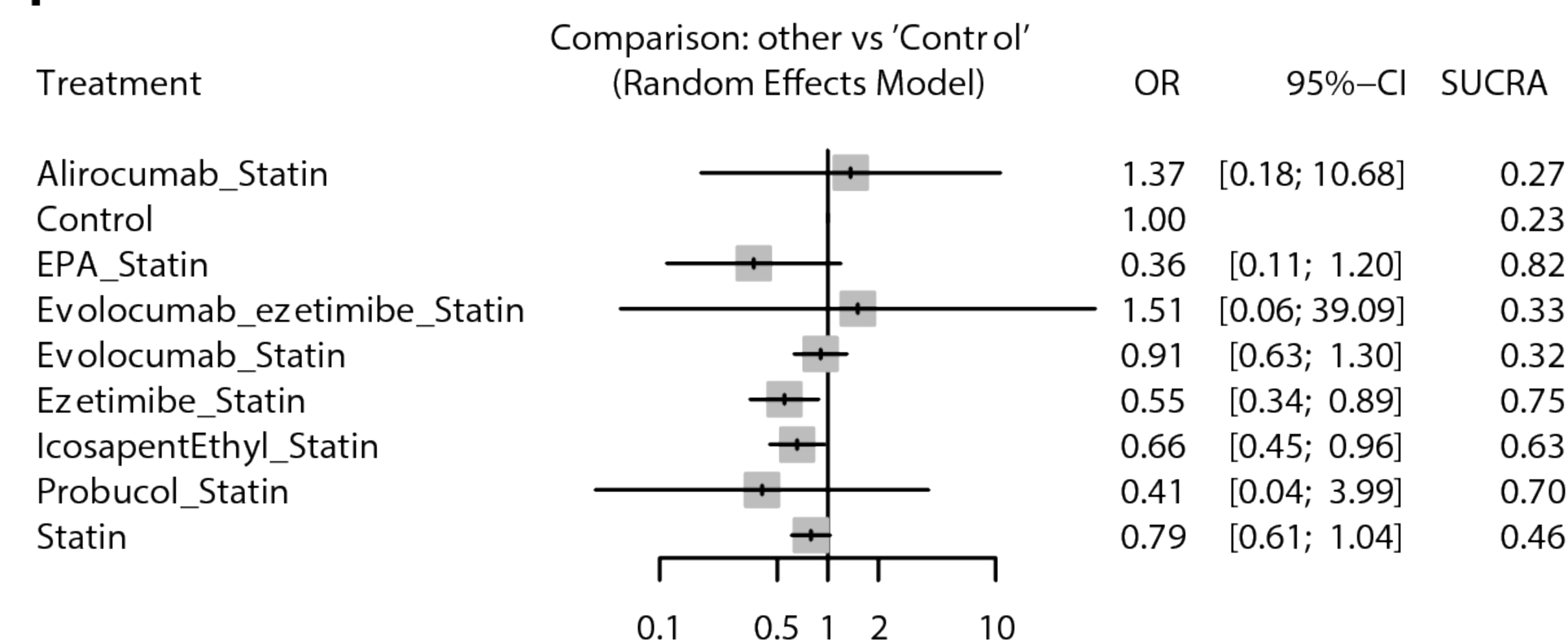
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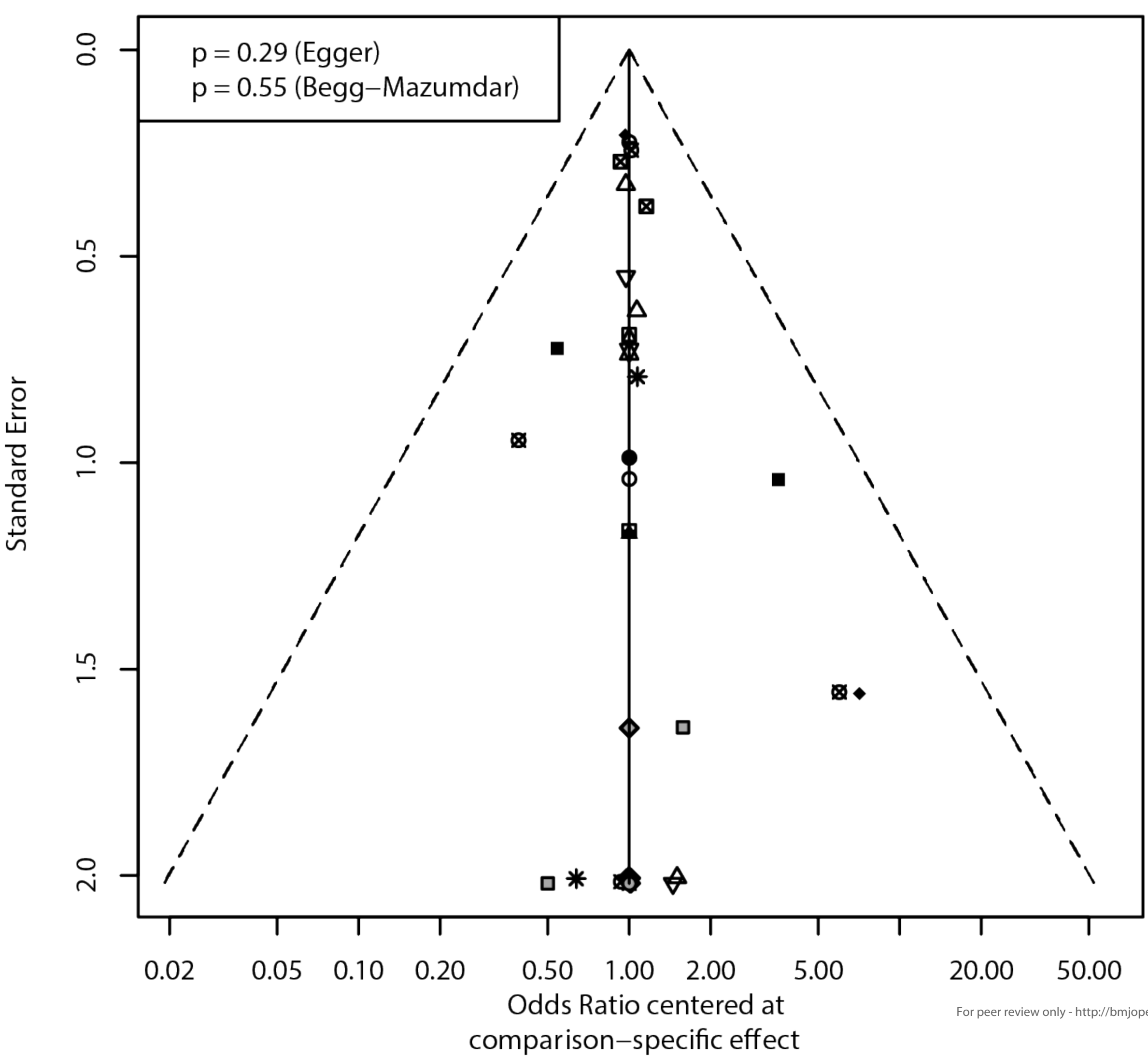


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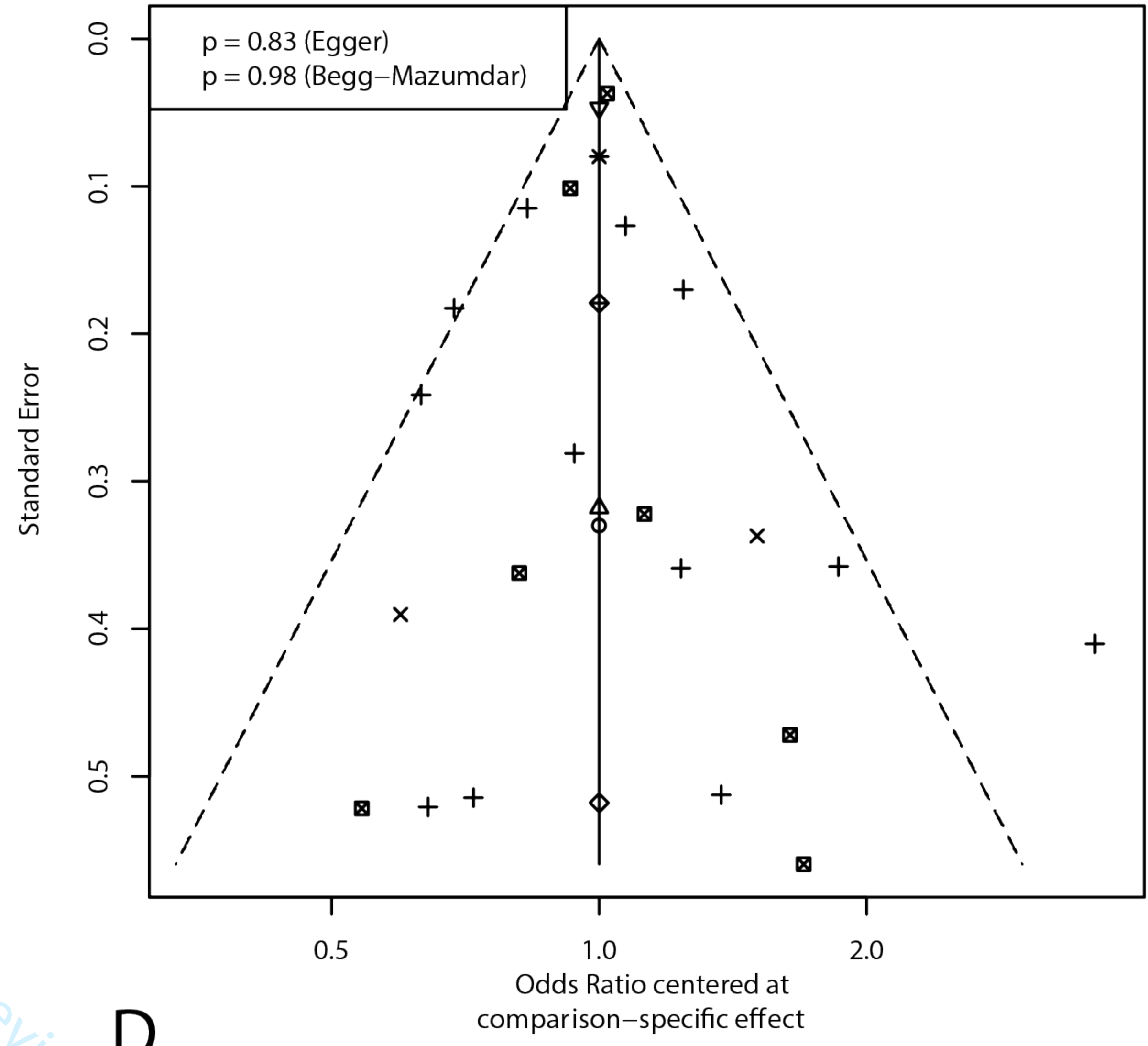


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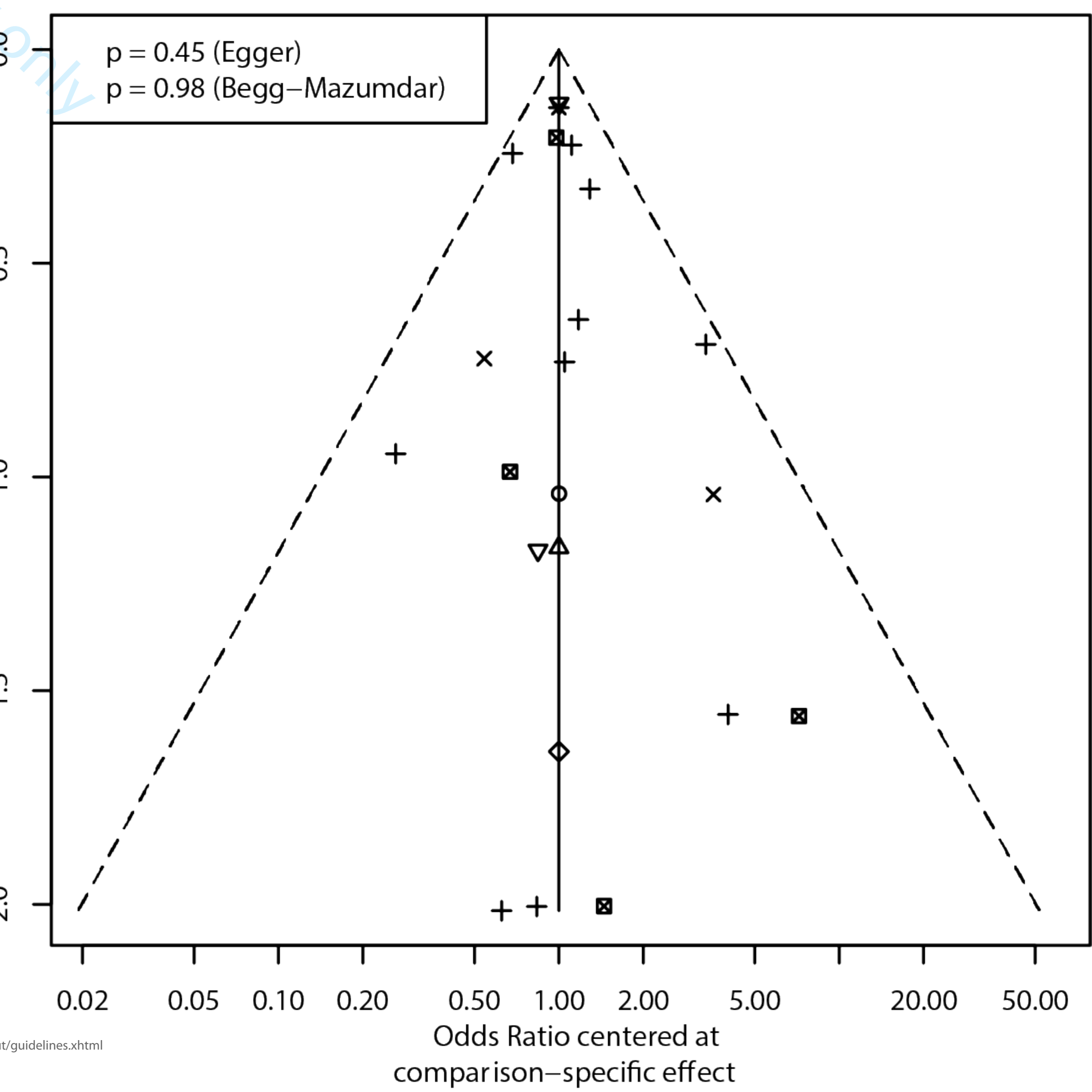
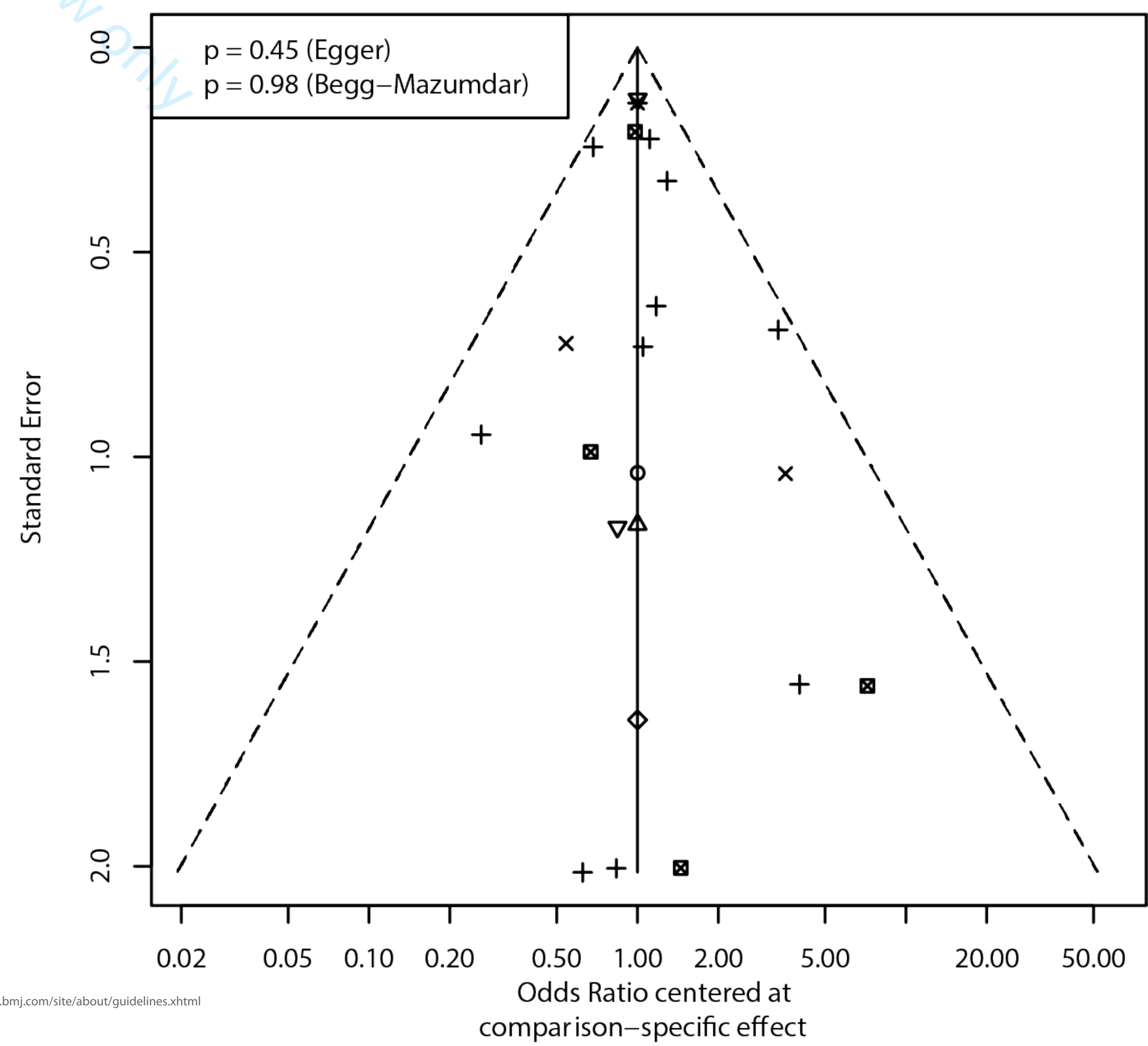
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The full search strategy for all databases.

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 'icosapentaenoic acid'/exp OR 'icosapentaenoic 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
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1		
2		
3	#1	19395
4	(Statin OR Simvastatin OR Rosuvastatin OR Atorvastatin OR	
5	Fluvastatin OR Lovastatin OR Pravastatin OR Pitavastatin or	
6	Mevastatin OR ezetimibe OR "Eicosapentaenoic Acid" OR "Icosapent	
7	Ethyl" OR "Bempedoic acid" OR Fibrate OR Bezafibrate OR Gemfibrozil	
8	OR Fenofibrate OR Ciprofibrate OR Evolocumab OR Alirocumab OR	
9	Evinacumab OR Volanesorsen OR Vupanorsen OR Pelacarsen OR	
10	Olezarsen OR Inclisiran OR Olpasiran OR Lipid-lowering)	
11		
12	#2	13623
13	"Percutaneous coronary intervention" OR "Coronary angioplasty"	
14	#3	1346916
15	Random* OR randomized	
16	#4	690
17	#1 AND #2 AND #3	

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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 <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	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 <i>synthesis methods, such as network meta-analysis</i> . Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed</i> . <i>Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity</i> . 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, <i>including mention of why a network meta-analysis has been conducted</i> .	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. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .	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

1		database, including any limits used, such that it could be	
2		repeated.	
3	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).
4			P.5-P.6
5	Data collection	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.
6	process		P.6-P.7
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.
8			P.6-P.7
9	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.
10			P.7
11	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.
12			P.7
13	Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>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.</i>
14			P.7
15	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:
16			<ul style="list-style-type: none"> • <i>Handling of multi-arm trials;</i> • <i>Selection of variance structure;</i> • <i>Selection of prior distributions in Bayesian analyses;</i> and • <i>Assessment of model fit.</i>
17			P.7
18	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.
19			P.7
20	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).
21			P.7
22	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:
23			<ul style="list-style-type: none"> • Sensitivity or subgroup analyses; • Meta-regression analyses; • <i>Alternative formulations of the treatment network;</i> and • <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i>
24			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. <i>Modified approaches may be needed to deal with information from larger networks.</i>	P.10-P.12
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>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.</i> 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, <i>P</i> 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, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i>).	<i>n/a</i>
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

1	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). <i>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).</i>	P.15
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8	Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P.16
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11	FUNDING			
12	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
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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

Journal:	<i>BMJ Open</i>
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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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1 **Effectiveness of lipid-lowering therapy on mortality and**
2 **major adverse cardiovascular event outcomes in patients**
3 **undergoing percutaneous coronary intervention: a network**
4 **meta-analysis of randomized controlled trials**

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15 **Abstract**

16 **Background**

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

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22 **Objective**

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4 23 This study assessed the benefits of different lipid-lowering regimens on the risk of
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6 24 MACEs and mortality in the post-PCI population by network meta-analysis.
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9 25 **Methods**

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11 26 Public databases, including PubMed, Embase, and the Cochrane Library, were
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14 27 searched from inception to August 2022. Randomized controlled trials (RCTs) on
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17 28 lipid-lowering regimens in post-PCI populations were included and analysed. The
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20 29 outcomes were the incidence of all-cause mortality and MACEs, whether reported as
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22 30 dichotomous variables or as hazard ratios (HRs).
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25 31 **Results**

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27 32 Thirty-nine RCTs were included. For MACEs, alirocumab plus rosuvastatin (OR:
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29 33 0.18; 95% CI: 0.07-0.44), evolocumab plus ezetimibe and statins (OR: 0.19; 95% CI:
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31 34 0.06-0.59), eicosapentaenoic acid (EPA) plus pitavastatin (HR: 0.67; 95% CI: 0.49-
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33 35 0.96), and icosapent ethyl plus statins (HR: 0.73; 95% CI: 0.62-0.86) had significant
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35 36 advantages and relatively high rankings. For mortality, rosuvastatin (OR: 0.30; 95%
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37 37 CI: 0.11-0.84), ezetimibe plus statins (OR: 0.55; 95% CI: 0.43-0.89) and icosapent
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39 38 ethyl plus statins (OR: 0.66; 95% CI: 0.45-0.96) had significant advantages compared
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45 39 to the control.
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48 40 **Conclusion**

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50 41 EPA, especially icosapent ethyl, plus statins had a beneficial effect on reducing the
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53 42 risk of MACEs and mortality in post-PCI patients. PCSK9is plus statins were able to
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56 43 reduce the risk of MACEs, but the risk of mortality remained unclear.
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58 44 **Key words:** lipid-lowering therapy, major adverse cardiovascular events, mortality,
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4 45 network meta-analysis
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7 46 **Strengths and limitations of this study**
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9 47 Only RCTs with high overall design quality were considered for inclusion.
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11 48 MACE and mortality were adopted as outcomes with little influence from subjective
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13 49 factors.

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16 50 this meta-analysis was based on the study level instead of the individual level.
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19 51 The criteria for defining MACEs varied among studies.
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22 52 Many included studies only reported dichotomous outcomes but did not report the HR
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24 53 results.
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28 55 **Introduction**
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30 56 Acute coronary syndrome (ACS) is a term used to refer to a range of conditions
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32 57 associated with acute myocardial ischaemia and/or infarction, which are usually due
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34 58 to coronary artery occlusion and acute ischaemic necrosis of the myocardium due to
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36 59 progression of coronary atherosclerotic lesions(1, 2). Emergency percutaneous
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38 60 coronary intervention (PCI) can quickly restore myocardial perfusion(3). Although
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40 61 the development of technological and procedural PCI has resulted in substantial
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42 62 improvements in clinical outcomes, recurrent coronary events may still occur after
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44 63 PCI(4).
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50 64 The view of "residual cardiovascular risk" was introduced because MACEs still
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52 65 occurs in some patients who underwent PCI during follow-up. PCI can treat focal
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54 66 manifestations of systemic progressive disease, but the residual risk of acute coronary
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56 67 syndrome is largely related to the systemic proatherosclerotic effect of poorly
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4 68 controlled cardiovascular risk factors(4). Lowering lipid levels, especially LDL-C,
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7 69 can halt the progression of coronary atherosclerosis and improve cardiovascular
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10 70 outcomes. Based on this view, it is believed that long-term optimal lipid-lowering
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12 71 therapy is effective in reducing long-term cardiovascular events after PCI. However,
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14 72 this view was still subject to challenges.

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20 74 Based on data from the “Korea Acute Myocardial Infarction Registry”, the proponents
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22 75 concluded that patients treated with statins had significantly lower rates of MACEs,
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24 76 all-cause death, and cardiac death during the 2-year follow-up period after PCI
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27 77 application(5). However, a study of postoperative follow-up of PCI patients enrolled
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30 78 in the Melbourne Interventional Group registry concluded that statins have no
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32 79 significant beneficial effect on MACEs after PCI(6). The controversy may be
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35 80 explained by two concepts: on the one hand, the optimal lipid reduction target may
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38 81 not be achieved by using single statins(7,8). On the other hand, long-term high-dose
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40 82 application of statins increases the risk of intracerebral haemorrhage and other side
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43 83 effects(9,10).

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48 85 There is a consensus on preloading high-dose statins to reduce MACEs in the
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50 86 perioperative period with PCI(11,12). However, there is still insufficient evidence for
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53 87 the continued application of lipid-lowering drugs to reduce the risk of long-term
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56 88 MACEs and mortality. This study assessed the benefits of different lipid-lowering
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58 89 regimens on the risk of MACEs and mortality in the post-PCI population by network
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4 90 meta-analysis.
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9 92 **Methods**

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11 93 This study was performed in accordance with the Preferred Reporting Items for

12
13 94 Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study was

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15 95 registered with PROSPERO (CRD 42018099600).
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19 96 **Patient and Public Involvement**

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21 97 None
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27 99 **Search strategy**

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29 100 Public literature databases, including PubMed, Embase, and the Cochrane Library,

30
31 101 were searched from inception to August 2022 without language restrictions using the

32
33 102 following search terms: (lipid-lowering or statin or simvastatin or rosuvastatin or

34
35 103 atorvastatin or fluvastatin or lovastatin or pravastatin or pitavastatin or mevastatin or

36
37 104 ezetimibe or “eicosapentaenoic acid” or “icosapent ethyl” or “bempedoic acid” or

38
39 105 fibrate or bezafibrate or gemfibrozil or fenofibrate or ciprofibrate or evolocumab or

40
41 106 alirocumab or evinacumab or volanesorsen or vupanorsen or pelacarsen or olezarsen

42
43 107 or inclisiran or olpasiran) and (“percutaneous coronary intervention” or “coronary

44
45 108 angioplasty”) and (random* or randomized or randomized). The details of the full

46
47 109 search strategy are listed in the Supplementary file. The references of relevant

48
49 110 systematic reviews and meta-analyses were also searched to avoid omissions. The two

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51 111 authors conducted literature retrieval independently, and any conflicts were resolved
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4 112 through discussion with the third author.
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9 114 **Inclusion and exclusion criteria**
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11 115 The literature was included if it met the following criteria: 1) the study adopted a
12
13 116 randomized controlled study design; 2) the study included patients who underwent
14
15 117 PCI surgery or reported the subgroup of the population that underwent PCI; 3) the
16
17 118 lipid-lowering regimen was applied to the population of the intervention group; 4) the
18
19 119 control group used a different lipid-lowering agent or regimen; and 5) the study
20
21 120 reported the outcome of mortality and/or MACEs. The exclusion criteria were as
22
23 121 follows: 1) as preloading of statins before PCI was shown to have clear benefits, to
24
25 122 determine whether application of lipid-lowering drugs after PCI also had beneficial
26
27 123 effects, this work excluded studies on the preloading application of lipid-lowering
28
29 124 drugs before PCI; and 2) although high-dose lipid-lowering agents, such as statins,
30
31 125 have a better lipid-lowering effect, long-term application may bring potential side
32
33 126 effects(9,13). Therefore, only studies in which all agents were considered to be
34
35 127 applied at reasonable doses were included, and dose–response studies were excluded.
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37 128 In addition, repeatedly published studies, protocols, conference abstracts, reviews,
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39 129 comments and editorials were also excluded.
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52 131 **Data extraction and quality assessment**
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54 132 Two authors independently extracted the information from the included studies. The
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56 133 contents include the name of the first author, publication year, study location, sample
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4 134 size (population that underwent PCI), study abbreviation and registration number,
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6 135 lipid-lowering intervention and control, and follow-up time.
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11 137 The outcomes analysed were the incidence of all-cause mortality and MACEs,
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13 138 whether reported as dichotomous or hazard ratio (HR) statistics based on Cox
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15 139 regression. The MACE outcome was selected to most closely approximate the
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17 140 composite endpoint, including mortality, MI, stroke, coronary revascularization, and
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19 141 restenosis. Study quality was assessed by two investigators using the Cochrane risk of
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21 142 bias assessment tool, which included random sequence generation, allocation
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23 143 concealment, blinding of participants and personnel, blinding of outcome assessment,
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25 144 incomplete outcome data, selective reporting, and other potential biases.
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35 146 Statistical analysis

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37 147 We conducted frequentist network meta-analysis (NMA) using random-effects
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39 148 models weighted by the inverse variance method. Odds ratios (ORs) and 95%
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41 149 confidence intervals (CIs) were used for dichotomous outcomes. The hazard ratios
42
43 150 (HRs) and 95% CIs based on Cox regression results were also pooled for reporting. If
44
45 151 the HR value was not reported but there was a Kaplan–Meier survival curve, the HR
46
47 152 value was extracted from the curve by GetData Graph Digitizer software version 2.24.
48
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51 153 In network plots, the direct comparisons among treatment arms are shown, the end of
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53 154 each line indicates a treatment arm, and the thickness of the lines indicates the number
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55 155 of studies comparing the two treatments. Forest plots were used to describe the
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4 156 network comparison results between each treatment and the control.
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7 157 The restricted maximum likelihood estimation was used to quantify network
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9 158 heterogeneity. The Q statistic was used to assess the sum of statistics for
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12 159 heterogeneity (within designs) and for overall inconsistency (between designs)(14).
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14 160 The ranking probabilities of each regimen were estimated using the surface under the
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16
17 161 cumulative ranking curve (SUCRA), which was the ratio of the area under the curve
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20 162 to the entire area. A comparison-adjusted funnel plot was used to examine potential
21
22 163 publication biases in the NMA. P values of less than 0.05 were considered to indicate
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25 164 statistical significance. The NMA was performed using R language with the
26
27 165 “netmeta” package.
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33 **Results**

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35 168 After removing duplicates, we obtained 1588 literature items. After screening the
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38 169 titles and abstracts, 1515 irrelevant studies were excluded. Seventy-three articles were
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40
41 170 screened for full text. The following articles were excluded: dose–response studies
42
43 171 (8); those where no PCI population or subgroup was reported (6); those where no
44
45
46 172 mortality or MACE-related outcomes were reported (6); repeated publications (5);
47
48
49 173 studies related to preloading of lipid-lowering agents (4); studies unrelated to lipid-
50
51 174 lowering agents (3); a protocol study (1); and a study with a non-RCT design (1).
52
53
54 175 Finally, 39 articles were included, containing 54478 post-PCI patients (15-53) (Figure
55
56 176 1).

57 58 **Table 1. The characteristics of included studies**

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Study	Location	Sample size	Abbreviation	Register ID	Intervention	Control	Follow-up#
Lorenz Råber 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	UMIN000000428	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	Pravastatin	2Y
Han Yaling 2009 [41]	China	1275	-	NCT00405717	Atorvastatin	Pravastatin	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]	Netherlands	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	-	Probuco;lovastatin	Placebo	6M
Haruhiko Onaka 1994 [52]	Japan	66	-	-	Pravastatin	Control	5M
Rakesh Sahni 1991 [53]	US	157	-	-	Lovastatin	Control	6M

178 Abbreviations: EPA: eicosapentaenoic acid.

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

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

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

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4 192 the other was based on taking statins as a whole. For the dichotomous results of
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6 193 MACEs, the NMA based on specific types of statins included 18 lipid-lowering
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9 194 regimens. The Q test for heterogeneity ($p = 0.07$) and inconsistency ($p = 0.16$) were
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11
12 195 nonsignificant, indicating no evidence of heterogeneity or inconsistency in the NMA.
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14 196 In pairwise comparisons with the control, alirocumab plus rosuvastatin (OR: 0.18;
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17 197 95% CI: 0.07-0.44; SUCRA: 0.94), evolocumab plus atorvastatin and ezetimibe (OR:
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20 198 0.18; 95% CI: 0.05-0.63; SUCRA: 0.90), and ezetimibe plus rosuvastatin (OR: 0.29;
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22 199 95% CI: 0.11-0.76; SUCRA: 0.80) had significant advantages and relatively high
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25 200 SUCRA rankings. No potential publication bias was found according to the
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28 201 comparison-adjusted funnel plot (Figure 3).
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32 203 In the NMA based on taking statins as a whole, ten regimens were analysed.
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35 204 Evolocumab plus ezetimibe and statins (OR: 0.19; 95% CI: 0.06-0.59; SUCRA: 0.92),
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38 205 alirocumab plus statins (OR: 0.27; 95% CI: 0.13-0.59; SUCRA: 0.87), and icosapent
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41 206 ethyl plus statins (OR: 0.39; 95% CI: 0.25-0.62; SUCRA: 0.72) had significant
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44 207 advantages and relatively high SUCRA rankings. No potential publication bias was
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51 210 For the HR results of MACEs, the NMA based on specific types of statins included
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54 211 nine regimens. The Q test for heterogeneity was nonsignificant ($p = 0.964$) because
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57 212 the network comparisons lacked loops. Therefore, the results were considered
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60 213 consistent. Compared to the control, eicosapentaenoic acid (EPA) plus pitavastatin

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4 214 (HR: 0.67; 95% CI: 0.49-0.96; SUCRA: 0.91), atorvastatin (HR: 0.76; 95% CI: 0.63-
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6 215 0.90; SUCRA: 0.83), and varespladib plus atorvastatin (HR: 0.77; 95% CI: 0.61-0.97;
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9 216 SUCRA: 0.77) had significant advantages and relatively high SUCRA rankings.
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12 217 Potential publication bias was not analysed due to the small number of included
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14 218 studies.

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19 220 In the NMA based on taking statins as a whole, seven regimens were analysed. EPA
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21 221 plus statins (HR: 0.60; 95% CI: 0.42-0.85; SUCRA: 0.96) and icosapent ethyl plus
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23 222 statins (HR: 0.73; 95% CI: 0.62-0.86; SUCRA: 0.81) had significant advantages over
24
25 223 the control.

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32 225 For the dichotomous mortality results, the NMA based on specific types of statins
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34 226 included 17 lipid-lowering regimens. The Q test for heterogeneity ($p = 0.78$) and
35
36 227 inconsistency ($p = 0.99$) were nonsignificant. Due to the rare occurrence of events, the
37
38 228 results of the comparison had low precision with a large standard error. Compared to
39
40 229 the control, only rosuvastatin (OR: 0.30; 95% CI: 0.11-0.84; SUCRA: 0.79) showed a
41
42 230 significantly better effect. Ezetimibe plus rosuvastatin had a relatively high SUCRA
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44 231 ranking, but there was no significant difference compared to the control (OR: 0.14;
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46 232 95% CI: 0.02-1.26; SUCRA: 0.86). No potential publication bias was found (Figure
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58 235 In the NMA based on taking statins as a whole, nine regimens were analysed.
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4 236 Ezetimibe plus statins (OR: 0.55; 95% CI: 0.43-0.89; SUCRA: 0.75) and icosapent
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6 237 ethyl plus statins (OR: 0.66; 95% CI: 0.45-0.96; SUCRA: 0.63) had significant
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8 238 advantages compared with the blank control group. No potential publication bias
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10 239 existed. NMA analysis was not performed due to the small number of studies
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12 240 reporting HRs for mortality (Figure 5).
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20 242 **Discussion**

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22 243 This study analysed the benefits of lipid-lowering therapy on mortality and MACE
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24 244 outcomes in patients who underwent PCI by network meta-analysis. The results
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26 245 showed that several lipid-lowering regimens could reduce the risk of MACEs
27
28 246 compared with the blank control. Icosapent ethyl plus statins had the benefit of
29
30 247 reducing both the risk of MACEs and mortality. However, EPA plus statins had more
31
32 248 advantages in reducing the risk of MACEs. Of note, based on the current evidence,
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34 249 alirocumab and evolocumab plus statins had obvious advantages in reducing the risk
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36 250 of MACEs but had no obvious benefit in reducing the risk of mortality.
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45 252 EPA is a long-chain omega-3 polyunsaturated fatty acid. Long-term intake of EPA
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47 253 can reduce the residual cardiovascular risk to reduce the risk of MACEs(54). In terms
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49 254 of pathological mechanisms, EPA combined with pitavastatin was shown to reduce
50
51 255 the lipid volume of coronary artery plaques and total atherosclerotic plaque volume in
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53 256 patients who underwent PCI, which may be the reason for the reduced risk of
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55 257 MACEs(55).
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6 259 Icosapent ethyl is a highly purified and stable eicosapentaenoic acid ethyl ester that
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9 260 has potential higher anti-inflammatory, antioxidant, plaque stability and cell
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11 261 membrane stability effects(56). In the NMA results, icosapent ethyl plus statins had
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14 262 significant benefits for reducing the risk of either mortality or MACEs in patients who
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17 263 underwent PCI, which was an ideal regimen for the population.
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22 265 Ezetimibe inhibits the absorption of cholesterol and has a synergistic lipid-lowering
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24 266 pharmacological effect with statins to further reduce the risk of death and MACEs. In
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26
27 267 particular, when combined with rosuvastatin, ezetimibe has a stronger lipid-lowering
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29
30 268 effect with a high safety profile without the risk of drug interactions(57). Our NMA
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33 269 results also showed that ezetimibe can reduce the risk of MACEs and mortality.

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35 270 According to the guidelines for the management of dyslipidaemia from the European
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38 271 Society of Cardiology and the European Atherosclerosis Society, ezetimibe was
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41 272 recommended if the LDL-C target was not reached(58,59). The American College of
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44 273 Cardiology guidelines also recommend adding ezetimibe when using maximally
45
46 274 tolerated statin therapy and if LDL-C levels remained ≥ 70 mg/dL(60). These benefits
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48 275 have also been demonstrated in the secondary prevention of PCI.
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53 277 Alirocumab and evolocumab are both proprotein convertase subtilisin/kexin type-9
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56 278 inhibitors (PCSK9is), which can increase the level of LDL receptor in the liver, thus
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59 279 improving the ability of the liver to bind LDL-C and reducing the level of peripheral
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4 280 LDL-C(61). There was also a synergistic lipid-lowering pharmacological effect when
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6 281 PCSK9is were combined with statins that resulted in a significantly reduced LDL-C
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9 282 concentration and atherosclerosis event risk; however, there was still controversy
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11 283 regarding the mortality risk reduction(62). It has been suggested that the powerful
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13
14 284 effect of PCSK9is on reducing LDL-C predisposes patients to hypocholesterolaemia,
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17 285 which will not increase the risk of cerebral haemorrhage. PCSK9is may be the
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19 286 preferred lipid-lowering agents in patients with elevated ICH risk (63-65). On the
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22 287 other hand, PCSK9is did not reduce serum inflammatory factors in one study,
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24
25 288 suggesting that they may not reduce the risk of residual inflammation in the post-PCI
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28 289 population(66).

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32 291 In the results of this study, lipid-lowering therapy strategies had general advantages in
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35 292 reducing MACE risk. However, for all-cause mortality, the advantage of lipid-
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38 293 lowering therapy was not obvious. Based on dichotomous outcomes of mortality,
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41 294 some strategies may even have a tendency to increase the mortality risk. This
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43
44 295 challenges the opinion that lipid-lowering therapy is recommended after PCI(67). A
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47 296 large sample size retrospective study suggests that statins can reduce the risk of all-
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50 297 cause death in patients with coronary artery disease undergoing PCI, regardless of
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53 298 individual cholesterol levels(68). Alternatively, the “lipid paradox” view has been
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56 299 proposed and indicates that higher levels of LDL-C and triglycerides on admission are
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59 300 associated with better clinical outcomes. Especially in patients with ST-elevation
60 301 myocardial infarction, lower LDL-C levels were associated with worse mortality

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4 302 outcomes(69). However, this view is also controversial(70).
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9 304 On the other hand, it is possible that the contribution of LDL-C reduction to the risk
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11 305 of mortality outcomes is obscured by other confounding factors. For example,
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14 306 inflammatory status may also have had an important impact on patient mortality risk.
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17 307 In a cohort of post-PCI patients with low LDL-C levels, residual inflammatory risk
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19 308 also had a significant effect on overall mortality(71). C-reactive protein can also
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22 309 predict long-term mortality in post-PCI patients independent of LDL-C levels(72). In
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25 310 addition, cardiac remodelling also has an important impact on the survival outcome of
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27 311 post-PCI patients(73).
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29
30 312 There are several limitations in this study. First, this analysis was based on the study
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32 313 level instead of the individual level, making it difficult to consider the individual
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35 314 confounding factors in the analysis. Second, two included studies did not specify the
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37
38 315 type of statins, so our study had to be analysed separately according to whether all
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40 316 statins were considered as a whole. Third, the criteria for defining MACEs varied
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43 317 among studies, which contributed to heterogeneity among the study results. Fourth,
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45 318 many included studies only reported dichotomous outcomes but did not report the HR
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48 319 results, resulting in missing relevant data for the analysis.
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56 322 In conclusion, the results of this study suggested that EPA, especially icosapent ethyl,
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58 323 plus statins had a beneficial effect on reducing the risk of MACEs and mortality in
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4 324 post-PCI patients. PCSK9is plus statins were able to reduce the risk of MACEs, but
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6 325 the effects on the risk of mortality remained unclear.
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12 329

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18
19 332

20 333 **Author contributions**

22 334 Chang-Jiang Deng completed the manuscript, Ju Yan, Ting-Ting Wu, Ying Pan, Ying-
23 335 Ying Zheng guided the data analysis and the production of the figures, Xian-Geng
24 336 Hou, Si-Fan Wang, Subinur Sirajidin, Mikereyi Aimaitijiang, Xiang Xie read and
25 337 approved the final manuscript.
26
27 338
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30

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33
34 341

35 342 **Availability of data and materials**

37 343 the datasets used or analysed during the current study are available from the
38 344 corresponding author on reasonable request.
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41 345

42 346 **Declarations**

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46 348 **Ethics approval and consent to participate**

47 349 This study does not involve human participants and ethical approval was not required.
48
49 350

50 351 **Consent for publication**

51 352 not applicable.
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56 354 **Competing interests**

57 355 The authors declare that they have no competing interests.
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14 668 **Figure 1.** Flowchart of the study selection process for eligible studies

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17 669 **Figure 2.** Methodological quality assessment of included studies

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19 670 **Figure 3.** Network plots of comparisons for major outcomes included in the analyses.

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22 671 A: dichotomous results of MACE based on specific types of statins; B: dichotomous
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24 672 results of MACE based on taking statins as a whole; C: hazard ratio results of MACE
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26 673 based on specific types of statins; D: hazard ratio results of MACE based on taking
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28 674 statins as a whole; E: dichotomous results of mortality based on specific types of
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30 675 statins; F: dichotomous results of mortality based on taking statins as a whole.

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33 676 **Figure 4.** Forest plots of lipid-lowering therapy compare to control for outcomes in
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35 677 network meta-analysis with SUCRA ranking results. A: dichotomous results of
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37 678 MACE based on specific types of statins; B: dichotomous results of MACE based on
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39 679 taking statins as a whole; C: hazard ratio results of MACE based on specific types of
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41 680 statins; D: hazard ratio results of MACE based on taking statins as a whole; E:
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43 681 dichotomous results of mortality based on specific types of statins; F: dichotomous
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45 682 results of mortality based on taking statins as a whole.

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48 683 **Figure 5.** The comparison-adjusted funnel plot for assessing all main outcomes. A:
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50 684 dichotomous results of MACE based on specific types of statins; B: dichotomous
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52 685 results of MACE based on taking statins as a whole; C: dichotomous results of

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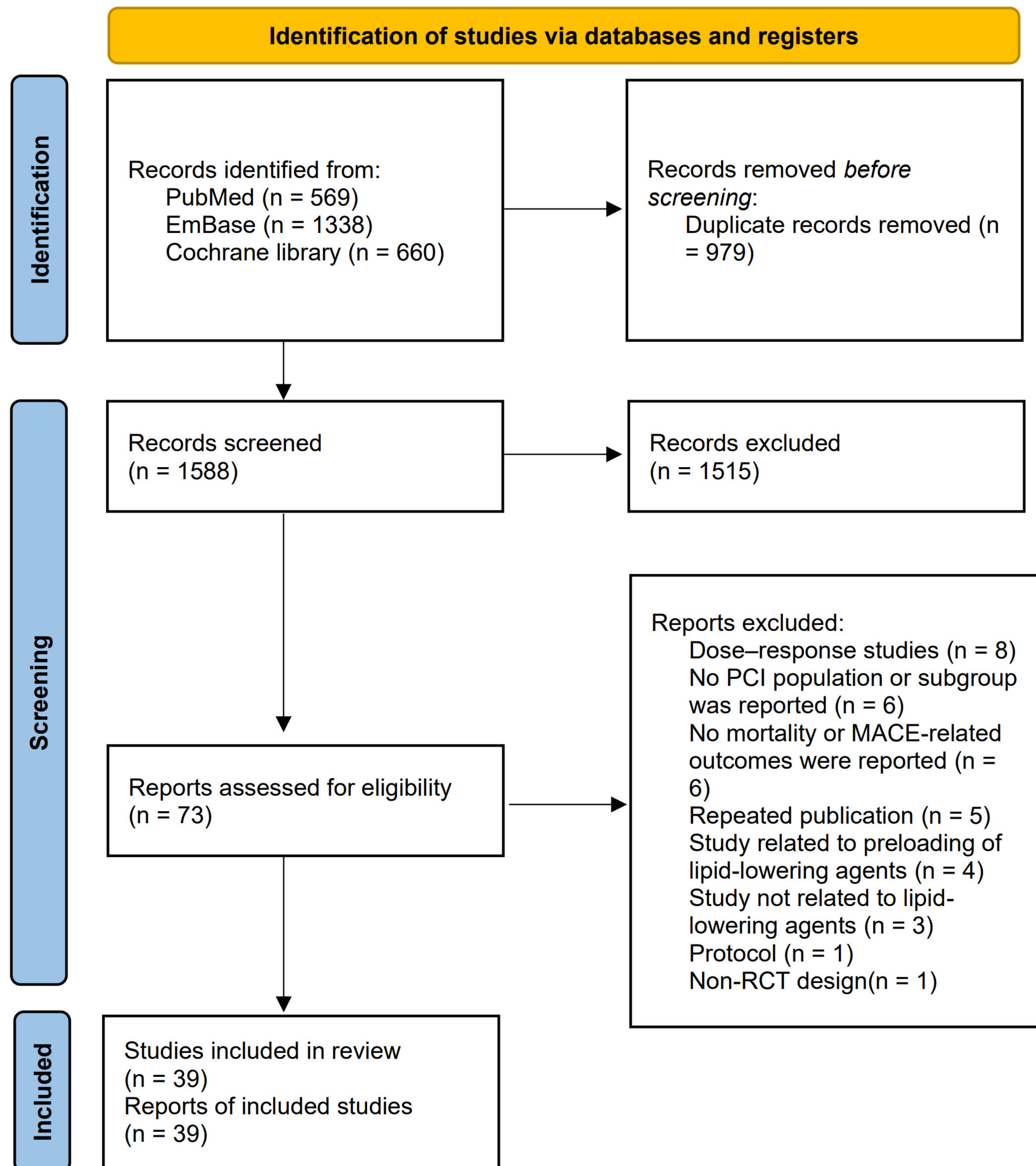
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PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



*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.

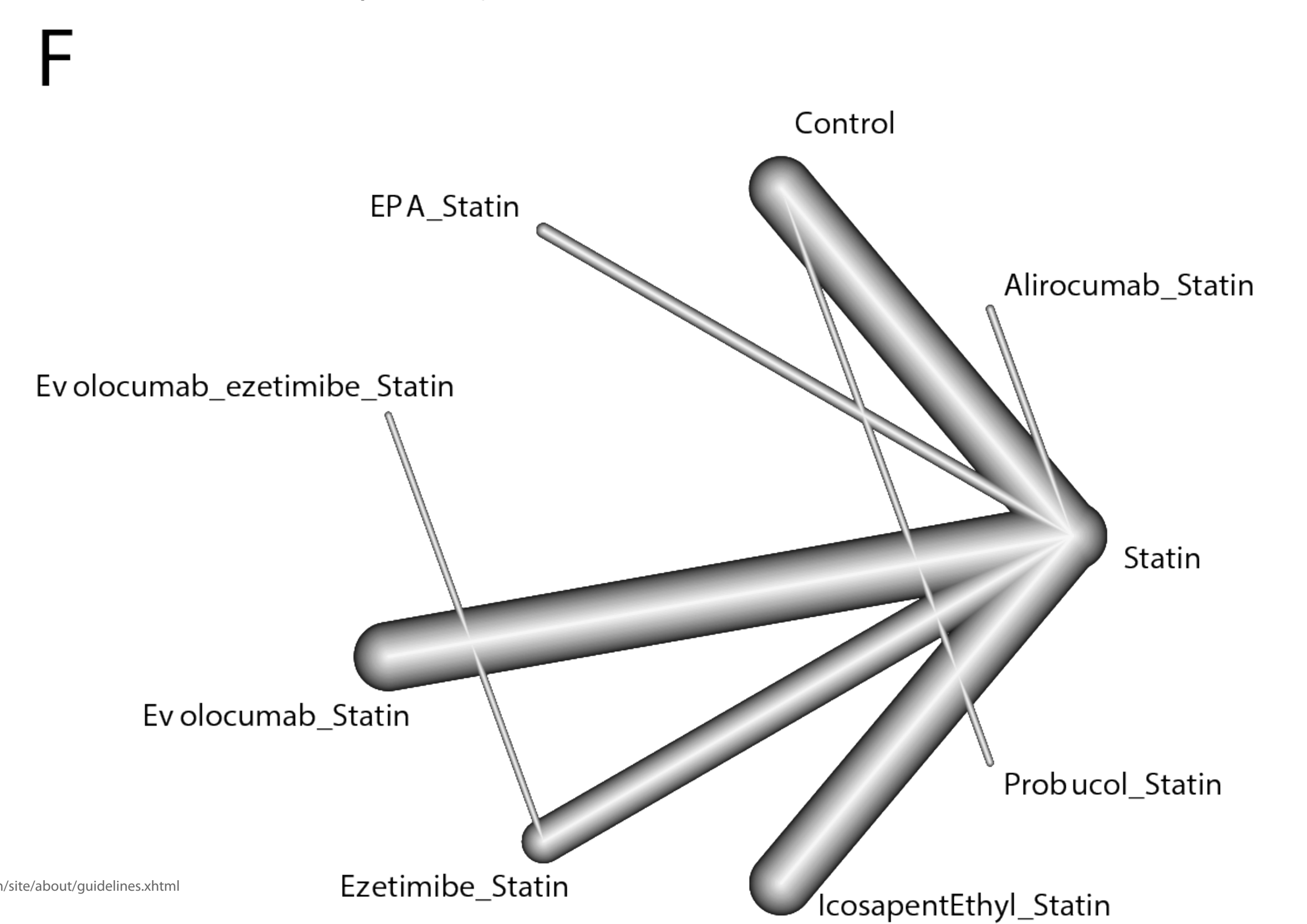
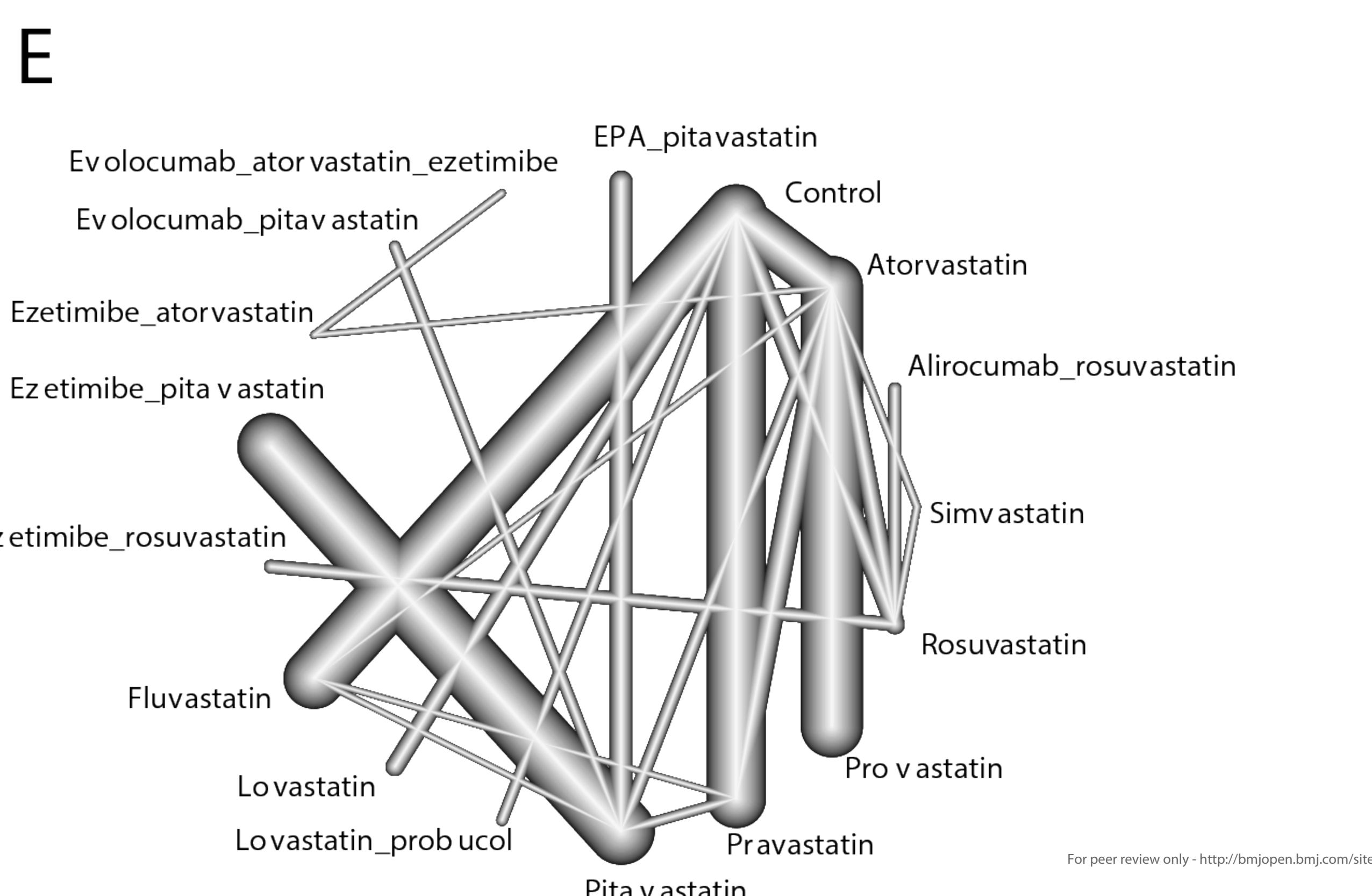
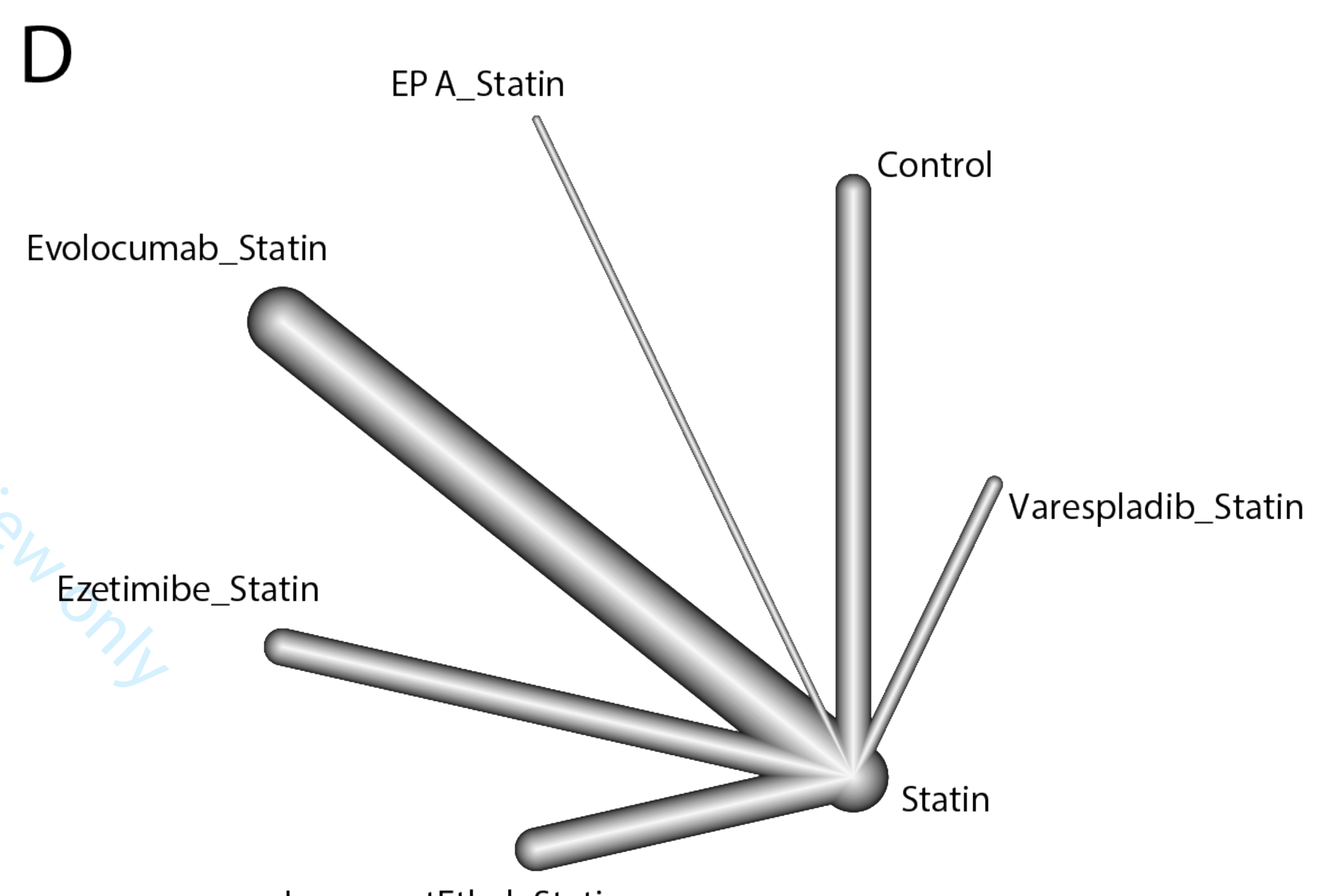
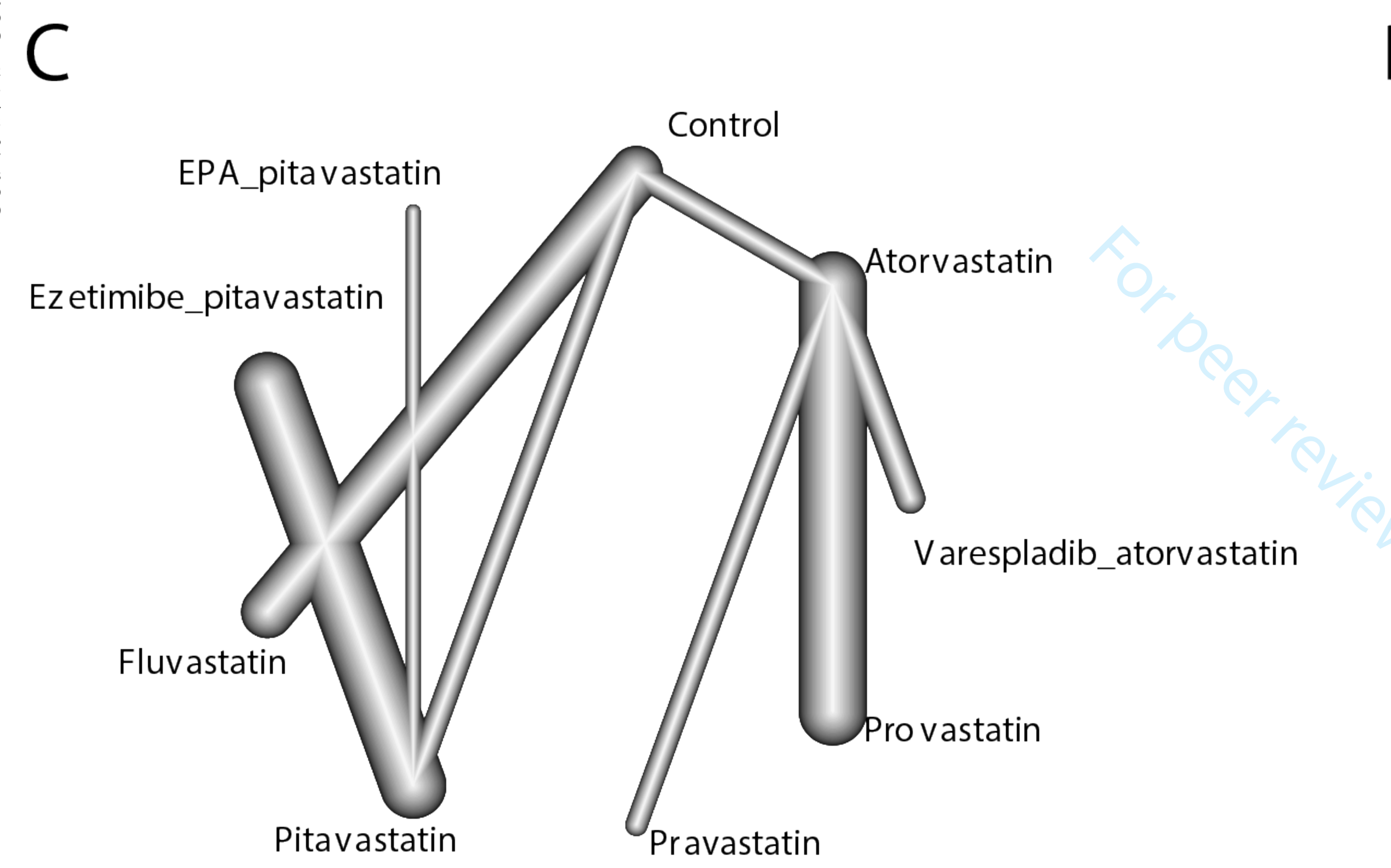
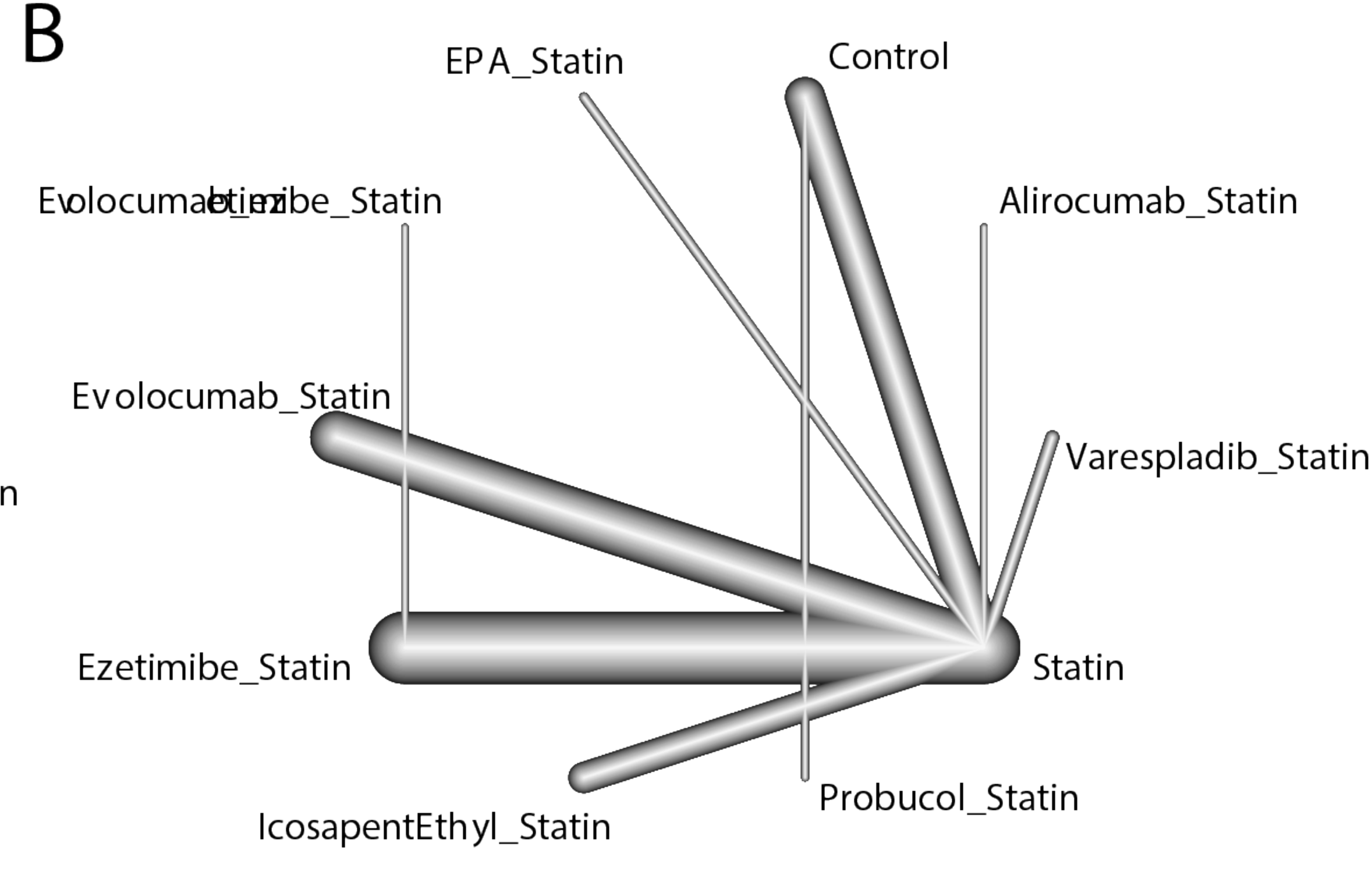
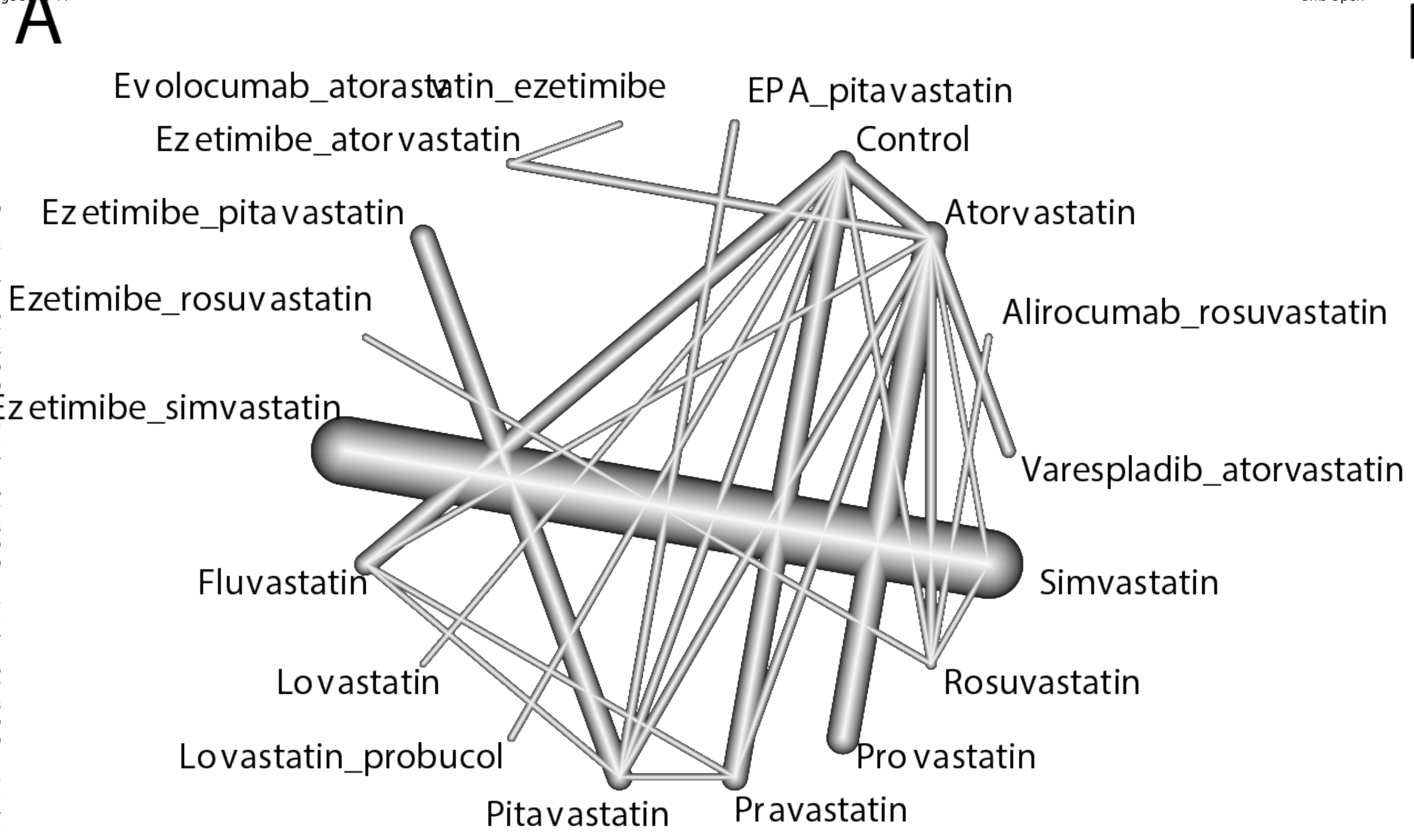
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

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

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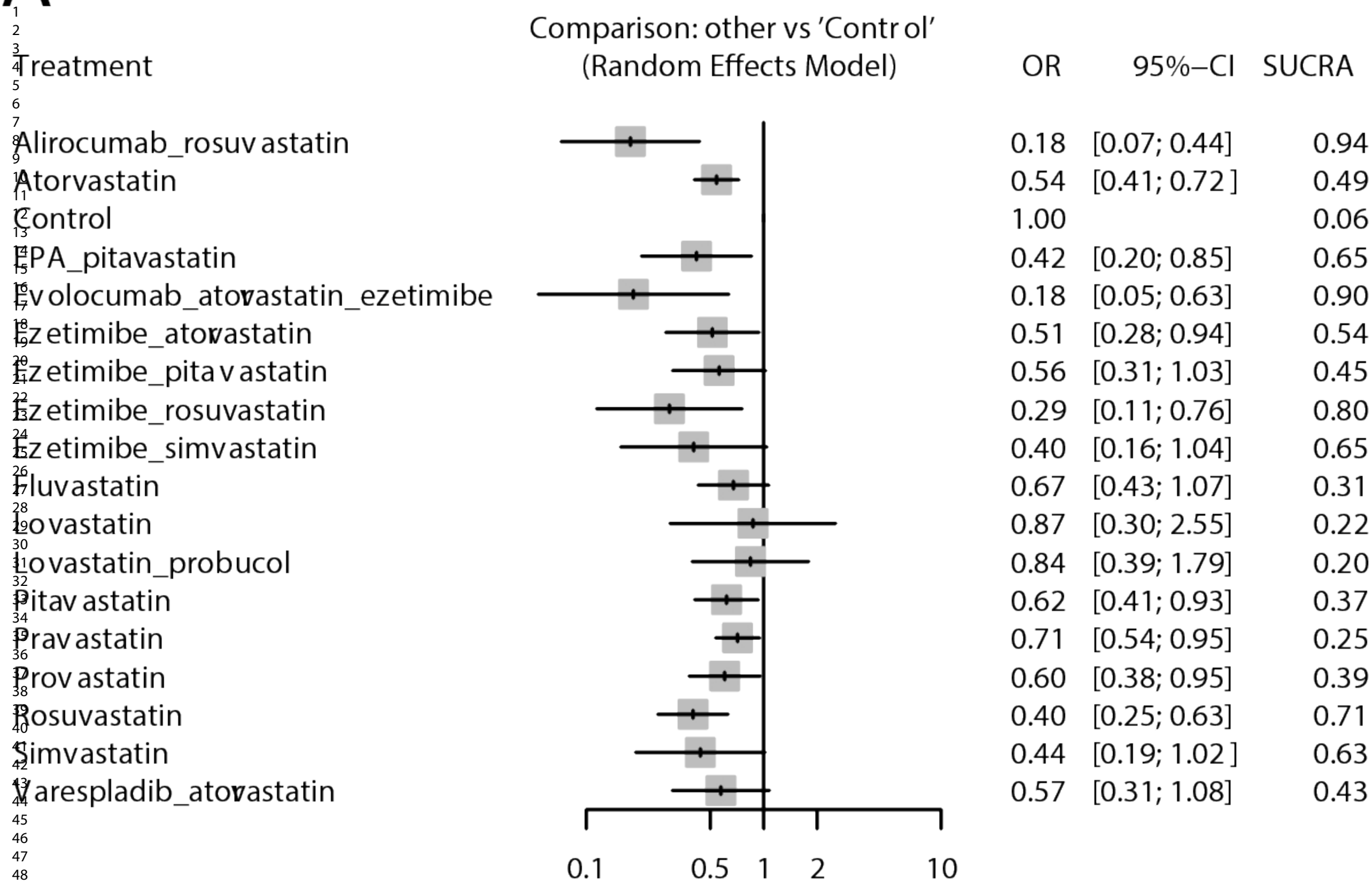
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bae JH 2004	?	?	-	-	+	?	+
C. Michael Gibson 2009	+	+	+	+	+	+	+
Christopher P Cannon 2015	+	+	+	+	+	+	+
Deng YF 2021	?	?	-	-	+	+	+
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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	+	+	-	-	+	?	+
J H O'Keefe Jr 1996	+	+	+	+	+	+	+
Kazumasa Nosaka 2016	+	?	-	+	+	+	+
Kenichi Tsujita 2015	+	+	-	+	+	+	+
Kensuke Matsushita 2016	?	?	-	-	+	+	+
Kiyoshi Hibi 2018	+	+	-	+	+	+	+
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Mario Leoncin 2014	+	?	-	-	+	+	+
MICHEL E. BERTRAND 1997	+	+	+	+	+	+	+
Patrick W J C Serruys 2002	+	+	+	+	+	+	+
Peterson, B. E. 2022	+	+	+	+	+	+	+
Rakesh Sahni 1991	?	?	-	-	+	+	+
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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	?	?	-	-	+	+	+
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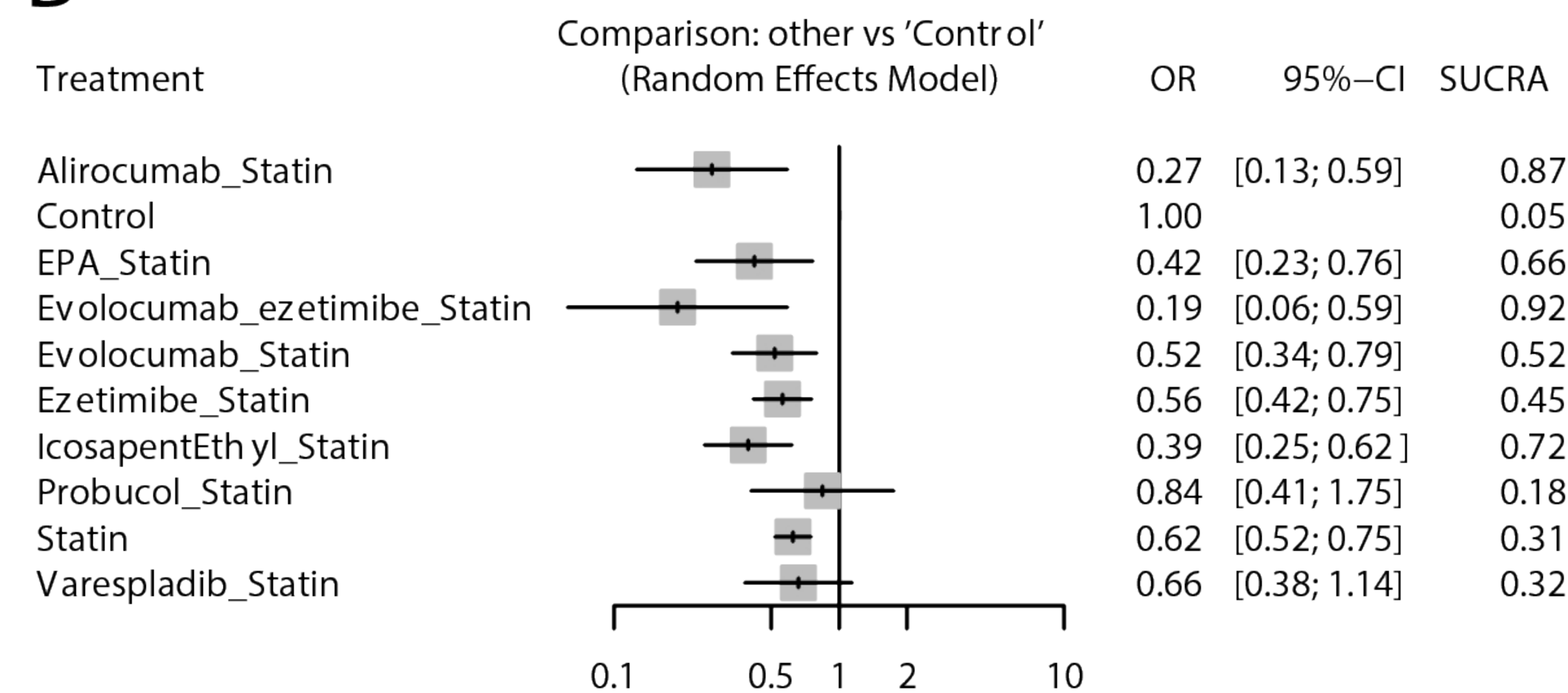


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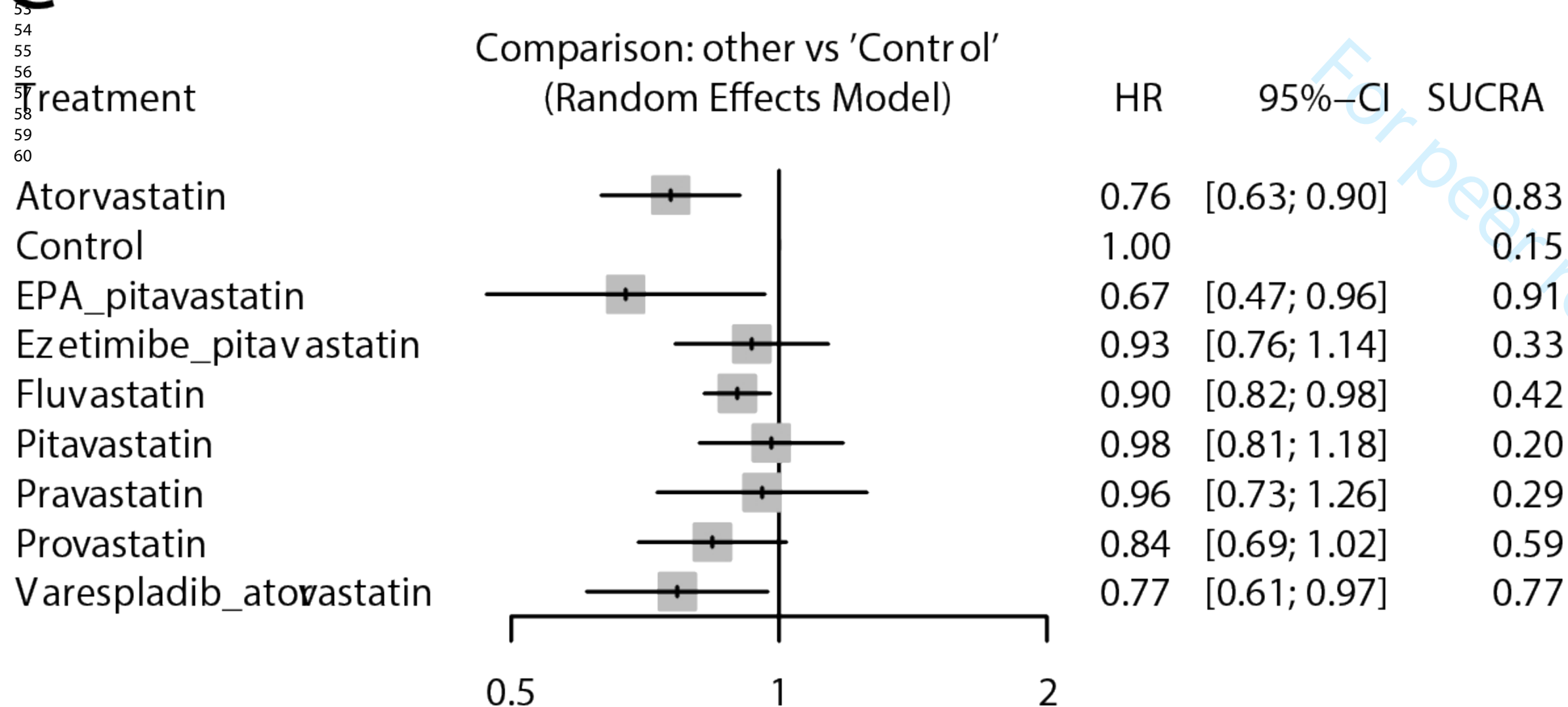
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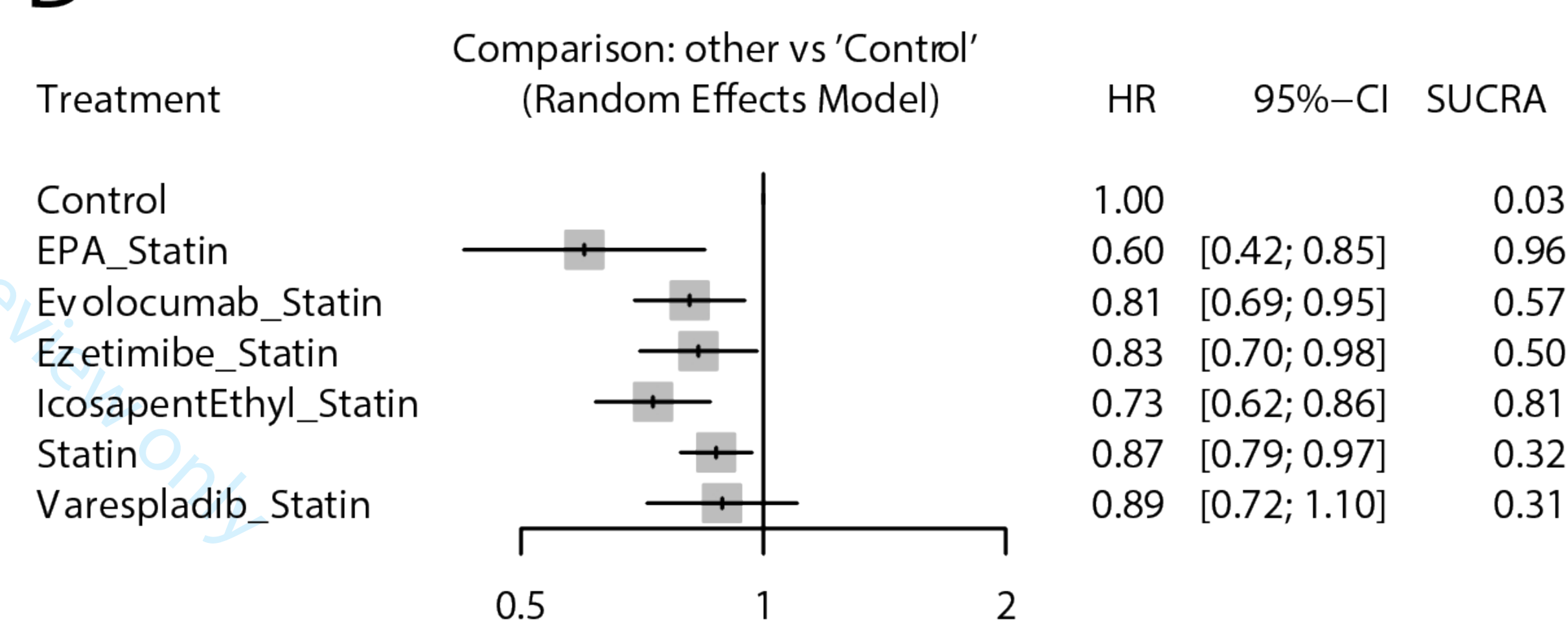
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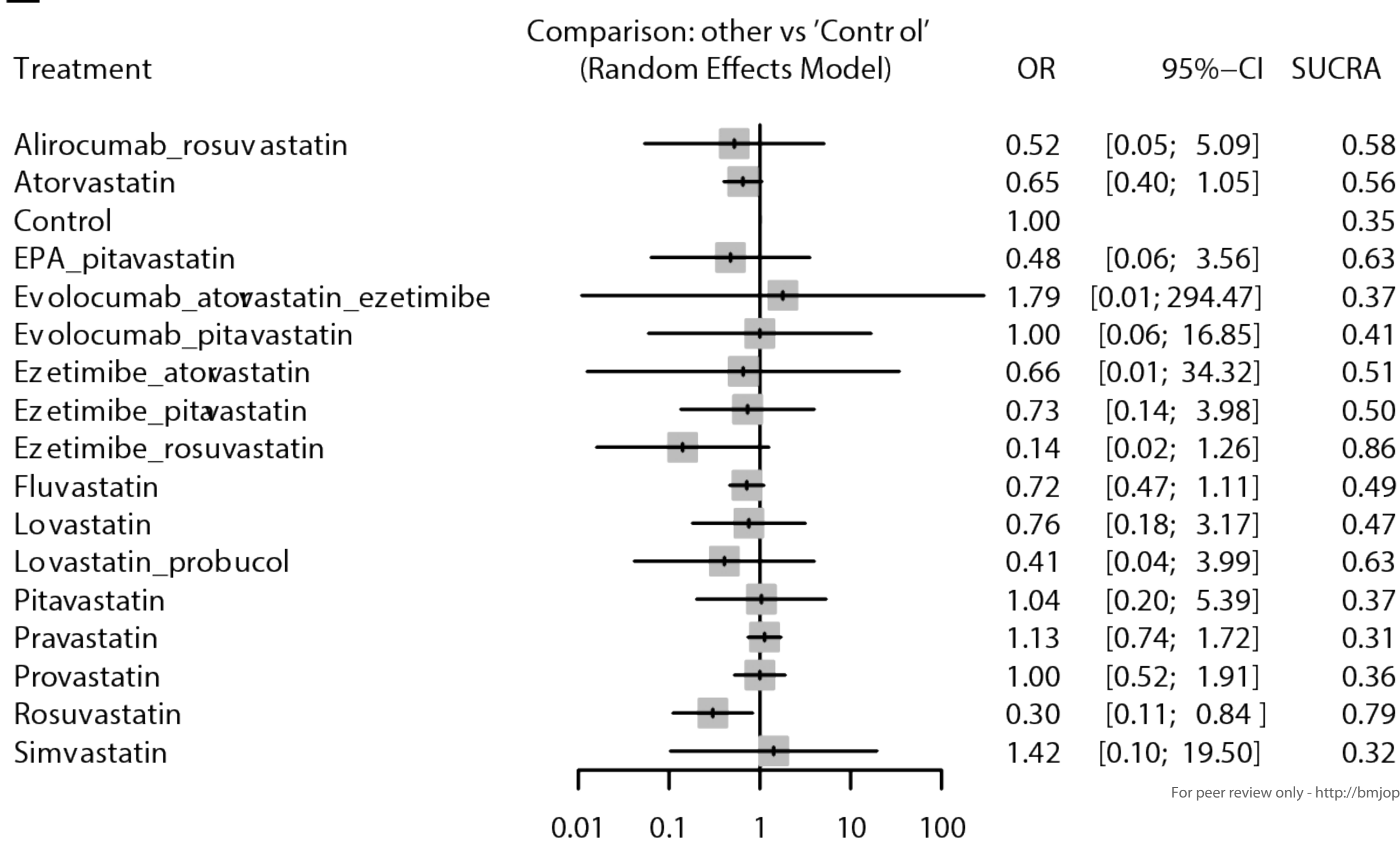
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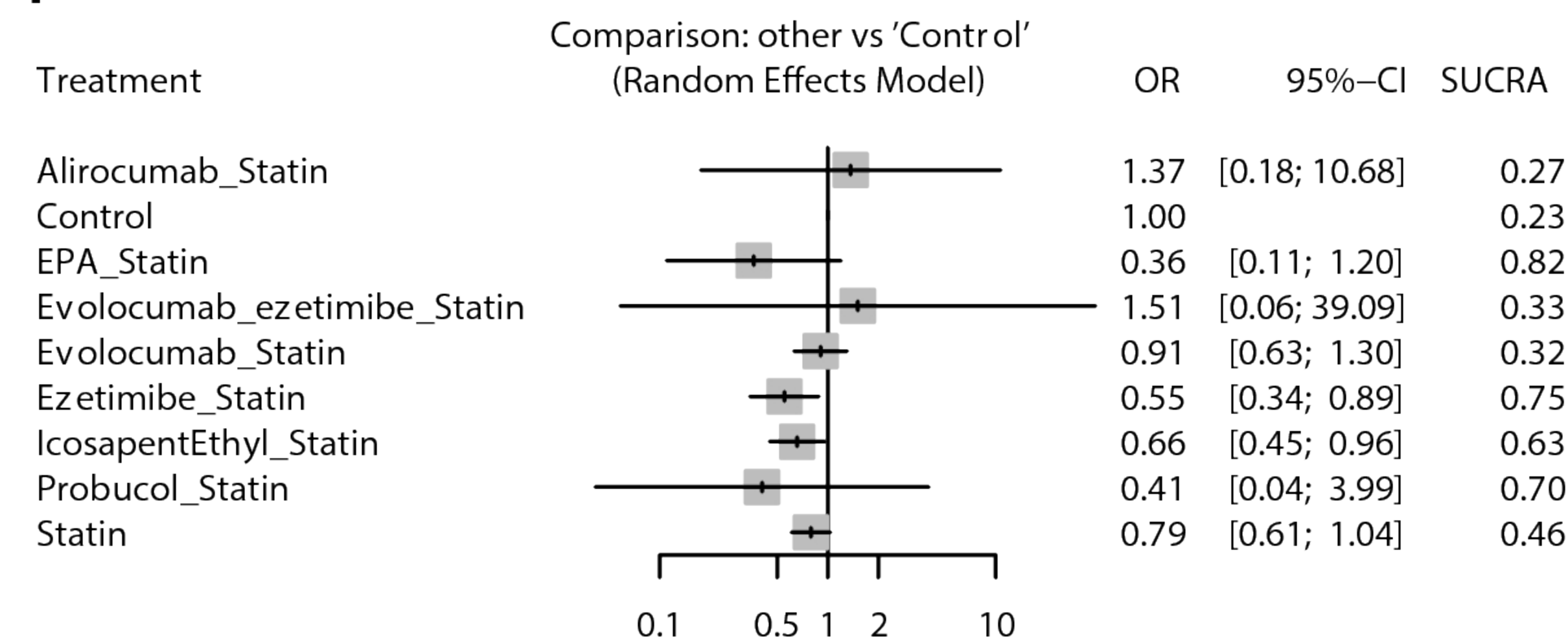
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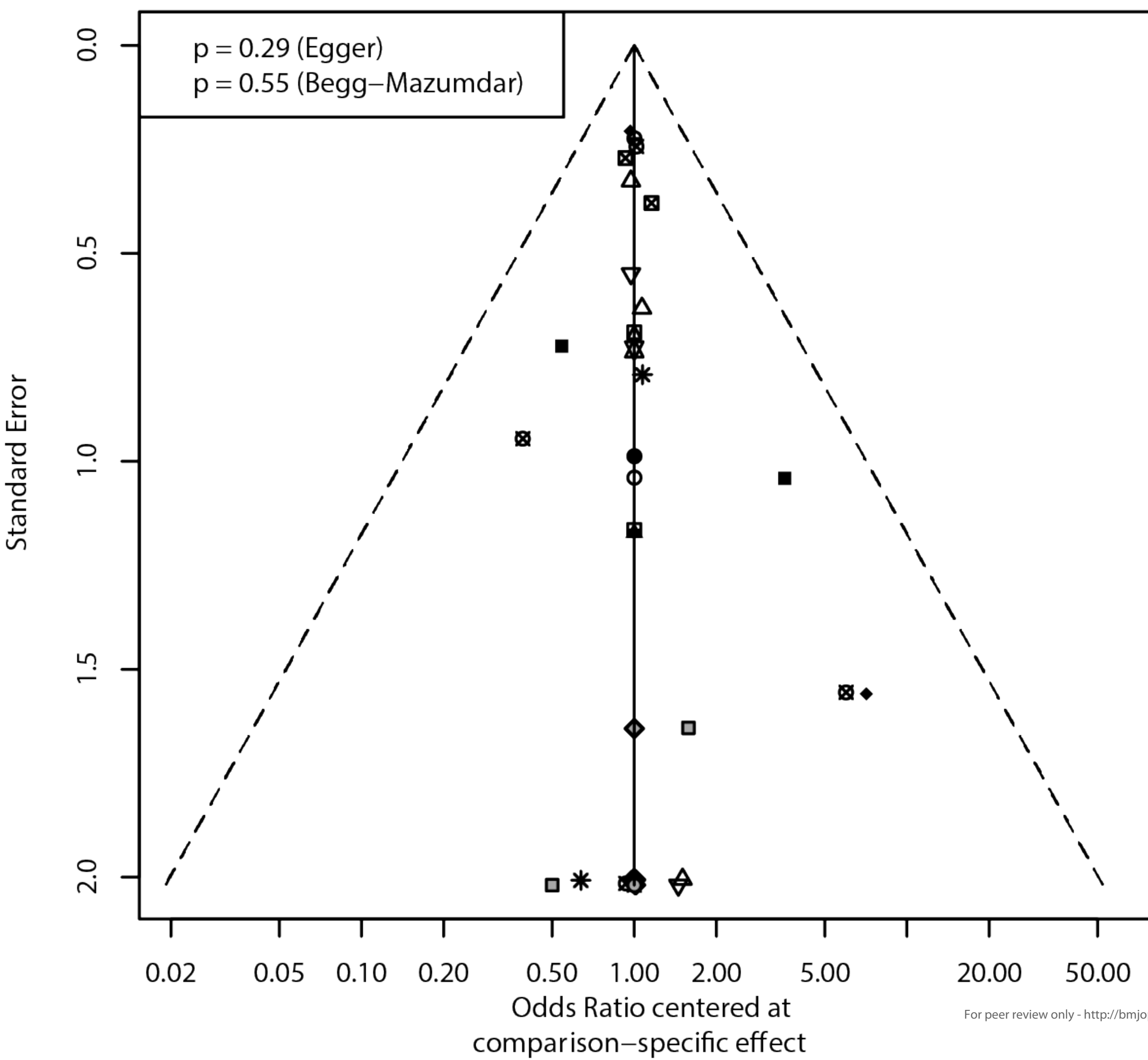


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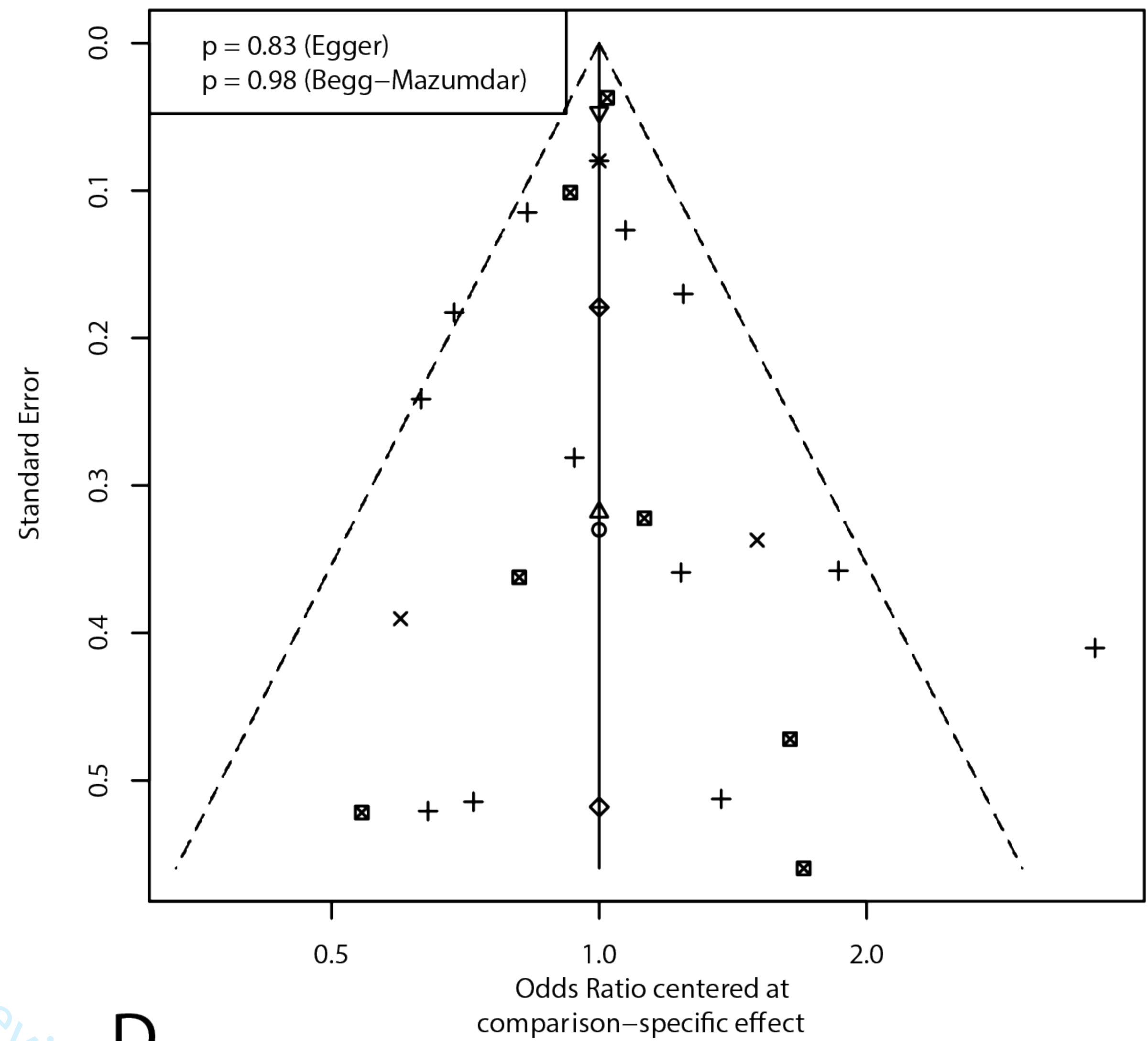


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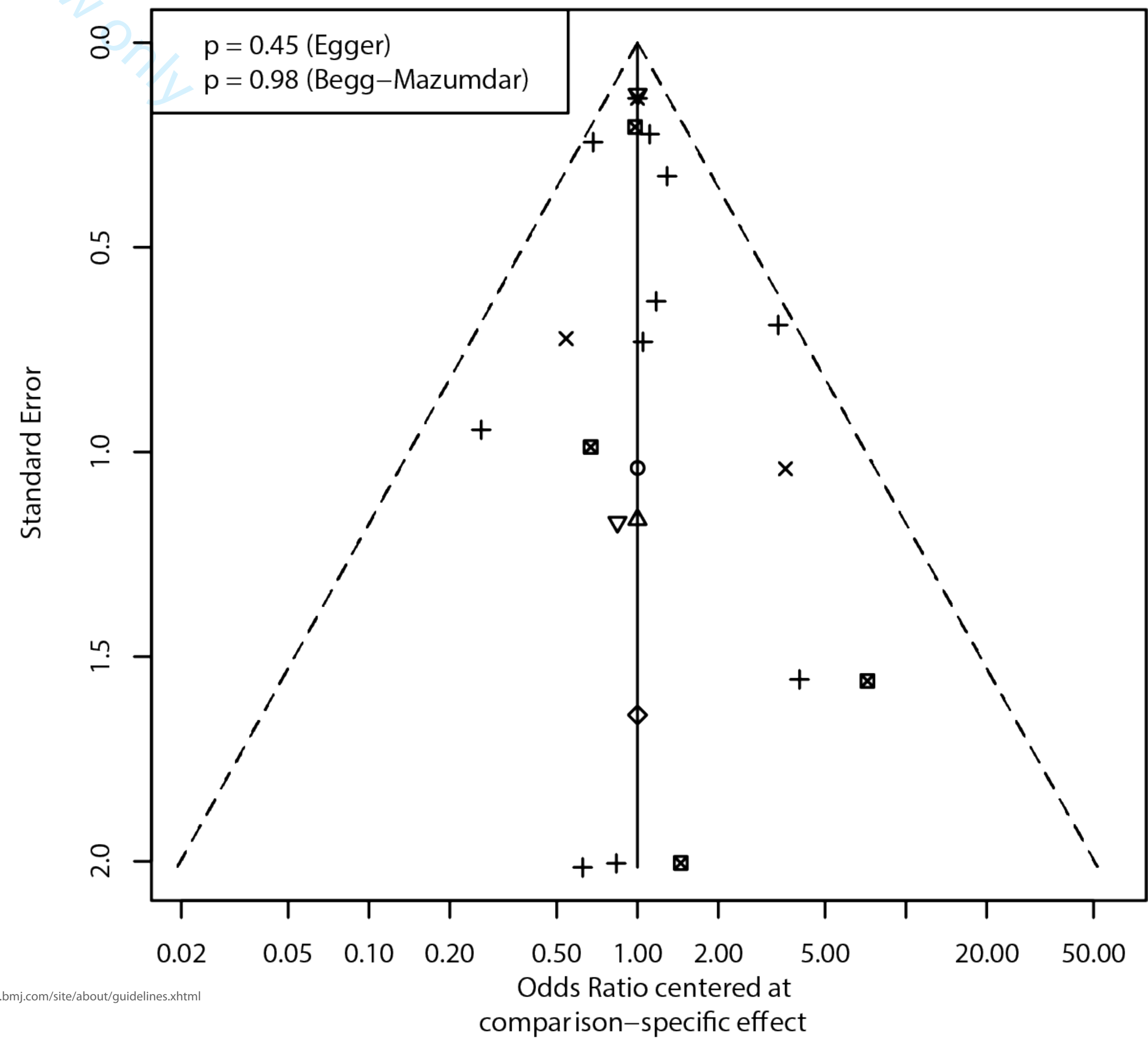
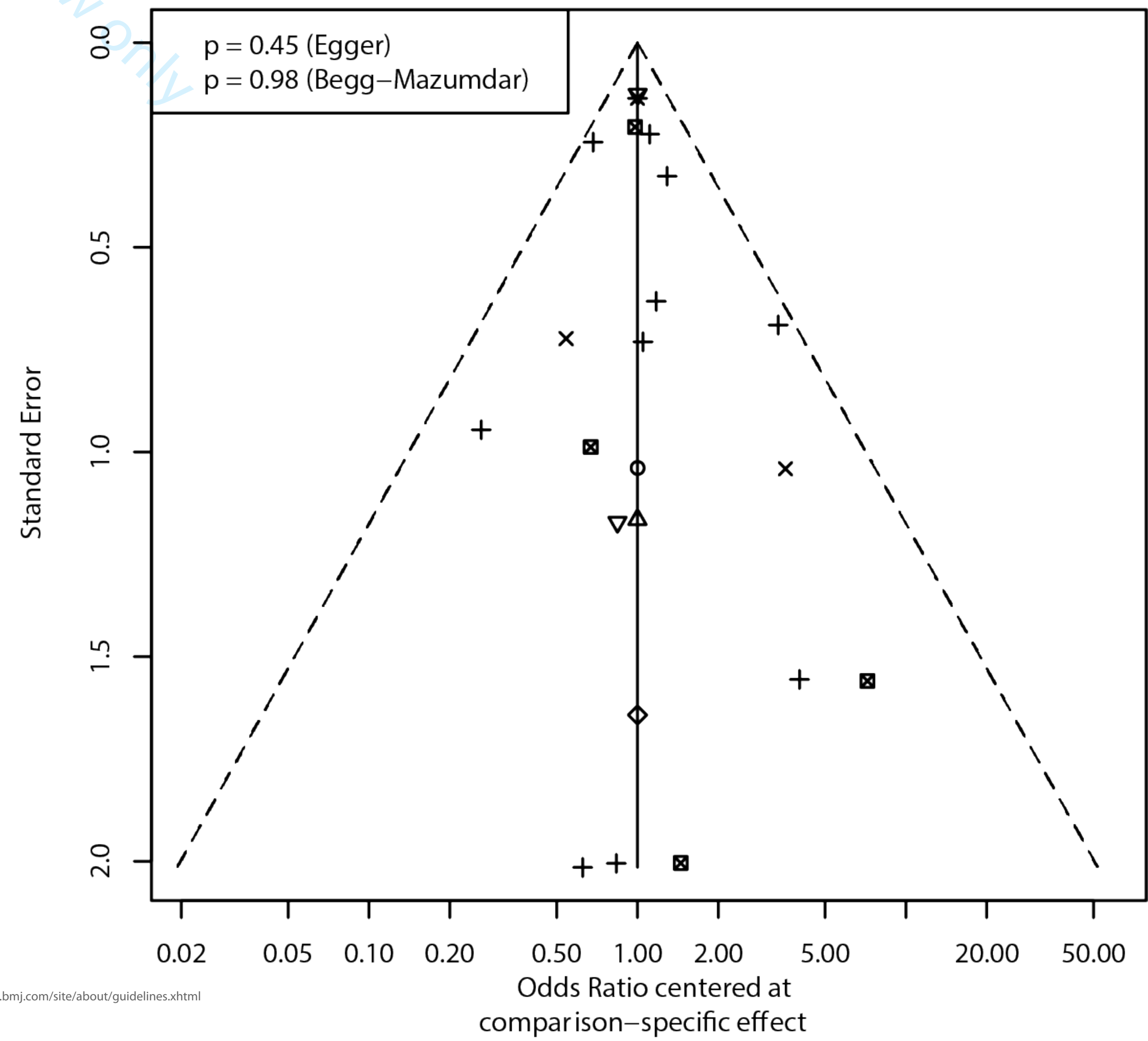
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D



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 'icosapentaenoic acid'/exp OR 'icosapentaenoic 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
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1		
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3	#1	19395
4	(Statin OR Simvastatin OR Rosuvastatin OR Atorvastatin OR	
5	Fluvastatin OR Lovastatin OR Pravastatin OR Pitavastatin or	
6	Mevastatin OR ezetimibe OR "Eicosapentaenoic Acid" OR "Icosapent	
7	Ethyl" OR "Bempedoic acid" OR Fibrate OR Bezafibrate OR Gemfibrozil	
8	OR Fenofibrate OR Ciprofibrate OR Evolocumab OR Alirocumab OR	
9	Evinacumab OR Volanesorsen OR Vupanorsen OR Pelacarsen OR	
10	Olezarsen OR Inclisiran OR Olpasiran OR Lipid-lowering)	
11		
12	#2	13623
13	"Percutaneous coronary intervention" OR "Coronary angioplasty"	
14	#3	1346916
15	Random* OR randomized	
16	#4	690
17	#1 AND #2 AND #3	

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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 <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	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 <i>synthesis methods, such as network meta-analysis</i> . Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed</i> . <i>Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> 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, <i>including mention of why a network meta-analysis has been conducted</i> .	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. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .	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

1		database, including any limits used, such that it could be		
2		repeated.		
3				
4	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
5				
6	Data collection	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
7	process			
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10	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
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12				
13	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
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19	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
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23	Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>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.</i>	P.7
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30	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: <ul style="list-style-type: none"> • <i>Handling of multi-arm trials;</i> • <i>Selection of variance structure;</i> • <i>Selection of prior distributions in Bayesian analyses; and</i> • <i>Assessment of model fit.</i> 	P.7
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38	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
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43	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
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46	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: <ul style="list-style-type: none"> • Sensitivity or subgroup analyses; • Meta-regression analyses; • <i>Alternative formulations of the treatment network; and</i> • <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i> 	<i>n/a</i>
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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. <i>Modified approaches may be needed to deal with information from larger networks.</i>	P.10-P.12
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>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.</i> 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, <i>P</i> 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, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i>).	<i>n/a</i>
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

1	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). <i>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).</i>	P.15
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8	Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P.16
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11	FUNDING			
12	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
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PICOS = population, intervention, comparators, outcomes, study design.