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SUPPLEMENTAL MATERIAL

Is the lower risk of venous thromboembolism with statins related to low-density-lipoprotein reduction?

A network meta-analysis and meta-regression of randomised controlled trials

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PRISMA NMA Checklist

Table S1: Patient population and references of the included studies

Study	PMID	First Author	Ref	Publication Year	Patient population	Prevention*
ASCOT-LLA	12686036	Sever	1	2003	Hypertension and other risk factors	Mixed
CARDS	15325833	Colhoun	2	2004	Type 2 diabetes and other risk factors	Primary
ASPEN	16801565	Knopp	3	2006	Type 2 diabetes	Mixed
LORD	20810109	Fassett	4	2010	Chronic kidney disease	-
4D	16034009	Wanner	5	2005	Type 2 diabetes undergoing haemodialysis	Mixed
-	16412856	Sola	6	2006	Non-ischaemic heart failure and left-ventricular ejection fraction $\leq 35\%$	-
ALLIANCE	15519006	Koren	7	2004	Coronary heart disease	Secondary
SALTIRE	15944423	Cowell	8	2005	Calcific aortic stenosis	Mixed
SPARCL	16899775	Amarenco	9	2006	Stroke or transient ischaemic attack and no coronary heart disease	Secondary
LEADe	20200346	Feldman	10	2010	Mild to moderate Alzheimer's disease	-
TNT	15755765	LaRosa	11	2005	Stable coronary heart disease	Secondary
PROVE IT-TIMI 22	15007110	Cannon	12	2004	Acute coronary syndrome	Secondary
REVERSAL	14996776	Nissen	13	2004	At least one coronary obstruction with luminal diameter narrowing of $\geq 20\%$	-
IDEAL	16287954	Pederson	14	2005	Myocardial infarction	Secondary
ASAP	11558482	Smilde	15	2001	Familial hypercholesterolaemia	Mixed
ALERT	12814712	Holdaas	16	2003	Renal transplant patients	Mixed
	15458450	Fellstrom	17	2004		
AFCAPS/TexCAPS	9613910	Downs	18	1998	Primary prevention population	Primary
MEGA	17011942	Nakamura	19	2006	Primary prevention population	Primary
LIPID	9841303	-	20	1998	Myocardial infarction or unstable angina	Secondary
PREVEND IT	15492322	Asselbergs	21	2004	Patients with microalbuminuria	Mixed
PROSPER	12457784	Sheperd	22	2002	Elderly patients with pre-existing vascular disease or at least one major risk factor	Mixed
	21342490	Freeman	23	2011		
CORONA	17984166	Kjekus	24	2007	Chronic NYHA class II, III, or IV heart failure	Mixed
GISSI-HF	18757089	Tavazzi	25	2008	Chronic NYHA class II, III, or IV heart failure	Mixed
HOPE-3	27040132	Yusuf	26	2016	Participants at intermediate cardiovascular risk	Primary
JUPITER	18997196	Ridker	27	2008	Primary prevention population	Primary
	19329822	Glynn	28	2009		
METEOR	17384434	Crouse	29	2007	Primary prevention population	Primary
ASTRONOMER	20048204	Chan	30	2010	Mild to moderate aortic disease	Primary
HPS	12114036	-	31	2002	Vascular disease or diabetes	Mixed
A-Z	15337732	deLemos	32	2004	Acute coronary syndrome	Secondary
SEARCH	21067805	Armitage	33	2010	Myocardial infarction	Secondary

PMID = PubMed ID; *prevalence of CVD in RCTs participants (only primary prevention participants, only secondary prevention, mixed)

References of the included studies

1. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; **361**(9364): 1149-58.
2. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; **364**(9435): 685-96.
3. Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). *Diabetes Care* 2006; **29**(7): 1478-85.
4. Fassett RG, Robertson IK, Ball MJ, Geraghty DP, Coombes JS. Effect of atorvastatin on kidney function in chronic kidney disease: a randomised double-blind placebo-controlled trial. *Atherosclerosis* 2010; **213**(1): 218-24.
5. Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005; **353**(3): 238-48.
6. Sola S, Mir MQ, Lerakis S, Tandon N, Khan BV. Atorvastatin improves left ventricular systolic function and serum markers of inflammation in nonischemic heart failure. *J Am Coll Cardiol* 2006; **47**(2): 332-7.
7. Koren MJ, Hunninghake DB, Investigators A. Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics: the alliance study. *J Am Coll Cardiol* 2004; **44**(9): 1772-9.
8. Cowell SJ, Newby DE, Prescott RJ, et al. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. *N Engl J Med* 2005; **352**(23): 2389-97.
9. Amarenco P, Bogousslavsky J, Callahan A, 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006; **355**(6): 549-59.
10. Feldman HH, Doody RS, Kivipelto M, et al. Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease: LEADe. *Neurology* 2010; **74**(12): 956-64.
11. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005; **352**(14): 1425-35.
12. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; **350**(15): 1495-504.
13. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA* 2004; **291**(9): 1071-80.
14. Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA* 2005; **294**(19): 2437-45.
15. Smilde TJ, van Wissen S, Wollersheim H, Trip MD, Kastelein JJ, Stalenhoef AF. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet* 2001; **357**(9256): 577-81.
16. Holdaas H, Fellstrom B, Jardine AG, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. *Lancet* 2003; **361**(9374): 2024-31.
17. Fellstrom B, Holdaas H, Jardine AG, et al. Effect of fluvastatin on renal end points in the Assessment of Lescol in Renal Transplant (ALERT) trial. *Kidney Int* 2004; **66**(4): 1549-55.
18. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998; **279**(20): 1615-22.
19. Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. *Lancet* 2006; **368**(9542): 1155-63.

20. Long-Term Intervention with Pravastatin in Ischaemic Disease Study G. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998; **339**(19): 1349-57.
21. Asselbergs FW, Diercks GF, Hillege HL, et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation* 2004; **110**(18): 2809-16.
22. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; **360**(9346): 1623-30.
23. Freeman DJ, Robertson M, Brown EA, et al. Incident venous thromboembolic events in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). *BMC Geriatr* 2011; **11**: 8.
24. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007; **357**(22): 2248-61.
25. Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; **372**(9645): 1231-9.
26. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease. *N Engl J Med* 2016; **374**(21): 2021-31.
27. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008; **359**(21): 2195-207.
28. Glynn RJ, Danielson E, Fonseca FA, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. *N Engl J Med* 2009; **360**(18): 1851-61.
29. Crouse JR, 3rd, Raichlen JS, Riley WA, et al. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. *JAMA* 2007; **297**(12): 1344-53.
30. Chan KL, Teo K, Dumesnil JG, Ni A, Tam J, Investigators A. Effect of Lipid lowering with rosuvastatin on progression of aortic stenosis: results of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. *Circulation* 2010; **121**(2): 306-14.
31. Heart Protection Study Collaborative G. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360**(9326): 7-22.
32. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 2004; **292**(11): 1307-16.
33. Armitage J, Bowman L, Wallendszus K, et al. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet* 2010; **376**(9753): 1658-69.

Table S2: Arm-specific rates of venous thromboembolism events

Drug, study	Dose (mg)	Follow-up (years)	Number of		Prevention	Rate, 95% CI (per 1000 person-years)
			Participants	Events		
ATORVASTATIN						
ASCOT-LLA	10	3.2	5168	13	Mixed	0.8 (0.4, 1.3)
ASPEN	10	4.3	948	4	Mixed	1.0 (0.3, 2.5)
CARDS	10	3.9	1428	14	Primary	2.5 (1.4, 4.2)
LORD	10	2.5	64	1	-	6.3 (0.2, 34.8)
TNT	10	4.9	5006	37	Secondary	1.5 (1.1, 2.1)
4D	20	3.9	619	13	Mixed	5.4 (2.9, 9.2)
Sola, 2006	20	1.0	54	3	-	55.6 (11.5, 162.4)
ALLIANCE	40	4.3	1217	9	Secondary	1.7 (0.8, 3.3)
ASAP	80	2.0	160	1	Mixed	3.1 (0.1, 17.4)
IDEAL	80	4.8	4439	33	Secondary	1.5 (1.1, 2.2)
LEADe	80	1.5	314	2	-	4.2 (0.5, 15.3)
PROVE IT-TIMI 22	80	2.0	2099	17	Secondary	4.0 (2.4, 6.5)
REVERSAL	80	1.5	328	0	-	0.0 (0.0, 7.5)
SALTIRE	80	2.2	77	0	Mixed	0.0 (0.0, 21.8)
SPARCL	80	4.9	2365	34	Secondary	2.9 (2.0, 4.1)
TNT	80	4.9	4995	47	Secondary	1.9 (1.4, 2.6)
FLUVASTATIN						
ALERT	40	5.1	1050	23	Mixed	4.3 (2.7, 6.4)
LOVASTATIN						
AFCAPS/TexCAPS	20-40*	5.3	3304	9	Primary	0.5 (0.2, 1.0)
PRAVASTATIN						
MEGA	10	5.3	3866	3	Primary	0.1 (0.0, 0.4)
LIPID	40	5.6	4512	79	Secondary	3.1 (2.5, 3.9)
PREVEND IT	40	3.8	433	3	Mixed	1.8 (0.4, 5.3)
PROSPER	40	3.2	2834	28	Mixed	3.1 (2.1, 4.5)
PROVE IT-TIMI 22	40	2.0	2063	16	Secondary	3.9 (2.2, 6.3)
REVERSAL	40	1.5	329	1	-	2.0 (0.1, 11.3)
ROSUVASTATIN						
CORONA	10	2.7	2514	15	Mixed	2.2 (1.2, 3.6)
GISSI-HF	10	3.9	2285	9	Mixed	1.0 (0.5, 1.9)
HOPE-3	10	5.6	6361	14	Primary	0.4 (0.2, 0.7)
JUPITER	20	1.9	8901	34	Primary	2.0 (1.4, 2.8)
ASTRONOMER	40	3.5	134	0	Primary	0.0 (0.0, 7.9)
METEOR	40	2.0	700	1	Primary	0.7 (0.0, 4.0)
SIMVASTATIN						
A-Z	20	2.0	2232	8	Secondary	1.8 (0.8, 3.5)
IDEAL	20	4.8	4449	37	Secondary	1.7 (1.2, 2.4)
SEARCH	20	6.7	6033	103	Secondary	2.5 (2.1, 3.1)
ASAP	40	2.0	165	0	Mixed	0.0 (0.0, 11.2)
HPS	40	5.0	10269	168	Mixed	3.3 (2.8, 3.8)
A-Z	80	2.0	2265	10	Secondary	2.2 (1.1, 4.1)
SEARCH	80	6.7	6031	90	Secondary	2.2 (1.8, 2.7)
PLACEBO						
4D	-	3.9	636	13	Mixed	5.2 (2.8, 9.0)
AFCAPS/TexCAPS	-	5.3	3301	12	Primary	0.7 (0.4, 1.2)
ALERT	-	5.1	1052	23	Mixed	4.3 (2.7, 6.4)
ALLIANCE	-	4.3	1225	10	Secondary	1.9 (0.9, 3.5)
ASCOT-LLA	-	3.2	5137	20	Mixed	1.2 (0.7, 1.9)
ASPEN	-	4.3	916	10	Mixed	2.5 (1.2, 4.7)
ASTRONOMER	-	3.5	135	1	Primary	2.1 (0.1, 11.8)
CARDS	-	3.9	1410	26	Primary	4.7 (3.1, 6.9)
CORONA	-	2.7	2497	28	Mixed	4.2 (2.8, 6.0)
GISSI-HF	-	3.9	2289	9	Mixed	1.0 (0.5, 1.9)
HOPE-3	-	5.6	6344	31	Primary	0.9 (0.6, 1.2)
HPS	-	5.0	10267	178	Mixed	3.5 (3.0, 4.0)
JUPITER	-	1.9	8901	60	Primary	3.5 (2.7, 4.6)
LEADe	-	1.5	326	1	-	2.0 (0.1, 11.4)
LIPID	-	5.6	4502	74	Secondary	2.9 (2.3, 3.7)
LORD	-	2.5	68	1	-	5.9 (0.1, 32.8)
MEGA	-	5.3	3966	1	Primary	0.0 (0.0, 0.3)
METEOR	-	2.0	281	0	Primary	0.0 (0.0, 6.6)
PREVEND IT	-	3.8	431	2	Mixed	1.2 (0.1, 4.4)
PROSPER	-	3.2	2865	20	Mixed	2.2 (1.3, 3.4)
SALTIRE	-	2.2	78	1	Mixed	5.8 (0.1, 32.5)
SPARCL	-	4.9	2366	29	Secondary	2.5 (1.7, 3.6)
Sola, 2006	-	1.0	54	2	-	37.0 (4.5, 133.8)

* Doses were 20mg and 40mg for each half of participants

Table S3: Assessment of risk of bias in individual studies

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting
4D	Low	Low	Low	Low	Unclear	Low
AFCAPS/TextCAPS	Low	Unclear	Low	Low	Unclear	Low
ALERT	Low	Unclear	Low	Unclear	Unclear	Low
ALLIANCE	Low	Unclear	High	Low	Unclear	Unclear
ASAP	Low	Unclear	Low	Low	Unclear	Low
ASCOT-LLA	Low	Low	High	Low	Unclear	Low
ASPEN	Low	Unclear	Low	Low	Unclear	Low
ASTRONOMER	Low	Low	Low	Unclear	Unclear	Low
A-Z	Low	Low	Low	Low	Unclear	Low
CARDS	Low	Low	High	Low	Unclear	Low
CORONA	Low	Low	High	Unclear	Unclear	Low
GISSI-HF	Low	Low	Low	Low	Unclear	Low
HOPE-3	Low	Low	Low	Low	Low	Low
HPS	Low	Low	High	Low	Unclear	Low
IDEAL	Unclear	Low	High	Low	Unclear	Low
JUPITER	Low	Unclear	Low	Unclear	Low	Low
LEADe	Low	Low	Low	Unclear	Unclear	Low
LIPID	Low	Unclear	Low	Low	Unclear	Low
LORD	Low	Low	Low	Unclear	Unclear	Low
MEGA	Low	Low	High	Low	Unclear	Low
METEOR	Low	Unclear	Low	Unclear	Unclear	Low
PREVEND IT	Low	Low	Low	Low	Unclear	Low
PROSPER	Low	Low	Low	Low	Unclear	Low
PROVE IT-TIMI 22	Unclear	Low	Low	Unclear	Unclear	Low
REVERSAL	Low	Low	Low	Low	Unclear	Low
SALTIRE	Low	Low	Low	Unclear	Unclear	Low
SEARCH	Low	Low	Low	Low	Unclear	Low
Sola, 2006	Low	Unclear	Low	Unclear	Unclear	Unclear
SPARCL	Low	Unclear	Low	Unclear	Unclear	Low
TNT	Unclear	Low	Low	Unclear	Unclear	Low
OVERALL	Low 27 (90.0%)	Low 20 (66.7%)	Low 23 (76.7%)	Low 18 (60.0%)	Low 2 (6.7%)	Low 28 (93.3%)
	Unclear 3 (10.0%)	Unclear 10 (33.3%)	Unclear 0 (0.0%)	Unclear 12 (40.0%)	Unclear 28 (93.3%)	Unclear 2 (6.7%)
	High 0 (0.0%)	High 0 (0.0%)	High 7 (23.3%)	High 0 (0.0%)	High 0 (0.0%)	High 0 (0.0%)

References of studies are reported in Table S1.

Figure S1: PRISMA Flow Diagram

Search Strategy

Studies published in any language were searched using PubMed, EMBASE, Web of Science, and Cochrane databases using relevant keywords. For PubMed, the combined terms were:

hydroxymethylglutaryl-coa reductase inhibitors [All Fields] OR anticholesteremic [All Fields] OR statin [All Fields] OR simvastatin [All Fields] OR hmg [All Fields] OR atorvastatin [All Fields] OR lovastatin [All Fields] OR pravastatin [All Fields] OR cerivastatin [All Fields] OR fluvastatin [All Fields] OR pitavastatin [All Fields] OR rosuvastatin [All Fields]

AND

venous thromboembolism [All Fields] OR pulmonary embolism [All Fields] OR thromboembolism [All Fields] OR VTE [All Fields] OR venous thrombosis [All Fields] OR deep vein thrombosis [All Fields] OR DVT [All Fields] OR pulmonary embolism [All Fields] OR embolism [All Fields] OR thrombosis [All Fields] OR vein thrombosis [All Fields]

The search was specifically translated for other databases.

Figure S2: Baseline covariates distribution

Standardised values of covariates are shown by pairwise comparisons of treatments
* Doses were 20mg and 40mg for each half of participants

Figure S3: Risk of venous thromboembolism for individual statins vs placebo

* Doses were 20mg and 40mg for each half of participants

Figure S4: Ranking probabilities of individual statins for the first three positions

* Doses were 20mg and 40mg for each half of participants

Figure S5: Ranking probabilities for individual statins

* Doses were 20mg and 40mg for each half of participants

Figure S6: Comparison-adjusted funnel plot

Each point indicates the difference between the study-specific estimate and its mean effect estimated (when possible) with random-effects pairwise meta-analysis

* Doses were 20mg and 40mg for each half of participants in the RCT

Figure S7: Association between risk of venous thromboembolism and sex or age

The plotted data show the relationship between risk of VTE and sex (left) or age (right), across studies. The dotted blue line indicates the predicted correlation and the solid black lines 95% confidence intervals. Each circle represents a randomised controlled trial and its size is proportional to the inverse of study variance. As indicated by the p-values, there was no association between the risk of VTE and sex or age.

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

Is the lower risk of venous thromboembolism with statins related to low-density-lipoprotein reduction?
A network meta-analysis and meta-regression of randomised controlled trials

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> .	Title Page
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. 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.	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> .	3
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
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.	4
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>	4
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.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Material
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
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
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.	5
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.	4, 5
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>	5
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> 	5

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.	5
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).	5
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> 	5, 6
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.	7, Figure S1
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Figure 1
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.	7
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.	7, Table 1, S1 and S2, Figure S2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	7, Table S3
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>	7, 8, Table 1, S1 and S2, Figure S3
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.	7, 8, Table 1, Figure 2, Figure S4 & S5
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.	8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Table S3, Figure S6
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>).	8, 9, Figure 2 & 3, Figure S7
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).	10, 11
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>	12, 13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	16, 17

PICOS = population, intervention, comparators, outcomes, study design. * Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement. † Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.