Brief Report

Statin Pretreatment and Microembolic Signals in Large Artery Atherosclerosis

A Systematic Review and Meta-Analysis

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Background and Purpose—Scarce data indicate that statin pretreatment (SP) in patients with acute cerebral ischemia because of large artery atherosclerosis may be related to lower risk of recurrent stroke because of a decreased incidence of microembolic signals (MES) during transcranial Doppler monitoring.

Methods—We performed a systematic review and meta-analysis of available observational studies reporting MES presence/absence or MES burden, categorized according to SP status, in patients with acute cerebral ischemia because of symptomatic (≥50%) large artery atherosclerosis. In studies with partially-published data, authors were contacted for previously unpublished information. We also performed a sensitivity analysis of studies with data on MES burden categorized according to SP status, and an additional subgroup analysis in patients receiving higher-dose SP (atorvastatin 80 mg or rosuvastatin 40 mg daily).

Results—Seven eligible study protocols were identified (610 patients, 54% with SP). SP was associated with a reduced risk of MES detection during transcranial Doppler monitoring (risk ratio=0.67; 95% CI, 0.45–0.98), with substantial heterogeneity between studies (I^2=52%). In studies reporting MES burden (n=4), a significantly lower number of MES were identified in patients with compared with those without SP (mean difference=−0.92; 95% CI, −1.64 to −0.19), with no evidence of heterogeneity between studies (I^2=49%). Subgroup analysis revealed that higher-dose SP reduced the risk of detecting MES (risk ratio=0.23; 95% CI, 0.06–0.88), with no evidence of heterogeneity between studies (I^2=0%).

Conclusions—SP seems to be associated with a lower incidence and burden of MES in patients with acute cerebral ischemia because of large artery atherosclerosis. **(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.118.021542.)**

Key Words: atherosclerosis ■ carotid stenosis ■ cerebral embolism ■ statins ■ transcranial doppler sonography

Microembolic signals (MES) are solid microparticles or microbubbles which are detected as high-intensity transient signals using transcranial Doppler ultrasound (TCD).[1] MES are frequently recorded in patients with acute cerebral ischemia (ACI) because of large artery atherosclerosis (LAA) and their presence is associated with a 10-fold increase in stroke recurrence in patients with symptomatic carotid stenosis.[2]

We have recently shown that statin pretreatment (SP) in ACI because of LAA was associated with fewer recurrent

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strokes, better early outcomes, and favorable functional outcome,[3] with this beneficial effect of SP potentially mediated through atherosclerotic plaque stabilization.[4]

We performed a systematic review and meta-analysis of available observational studies in patients with ACI because of LAA reporting detection of MES on TCD monitoring in patients with and without SP.

Methods

Authors declare that all supporting data are available within the article and in the online-only Data Supplement. This meta-analysis has adopted the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses),[5] whereas also adheres to the American Heart Association Journals' implementation of the Transparency and Openness Promotion guidelines. We used the Newcastle-Ottawa Scale to assess the quality of each nonrandomized study included in our meta-analyses.[6]

The corresponding risk ratios for identifying MES during TCD monitoring in patients with SP (SP+) versus patients without SP (SP−) were calculated. Where applicable, we also calculated the mean differences in the reported absolute MES numbers during TCD monitoring between SP+ and SP− groups, and the corresponding risk ratios of finding MES in patients with higher-dose SP compared with SP− patients. Statin higher dosage was defined as the maximum approved dose by the European Medicines Agency (80 mg per day for atorvastatin, simvastatin, fluvastatin, lovastatin, or pravastatin, and 40 mg per day for rosuvastatin).[4]

A random-effects model (DerSimonian-Laird) was used to calculate the pooled effect estimates. Heterogeneity between studies was assessed with the Cochran Q and I^2 statistics, with I^2 values of at least 50% considered to represent substantial heterogeneity and values of at least 75% indicative of considerable heterogeneity.[7] Publication bias was evaluated with both funnel plot inspection and the Egger linear regression test with $P<0.10$ significance level.

All statistical analyses were conducted using Review Manager (RevMan) Version 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Selection of the 7 eligible studies[4,8–13] is presented in Figure 1 and described in detail in the online-only Data Supplement. All required data were available in 3 original publications.[4,11,13] The corresponding authors from 4 of the 7 included studies were contacted to obtain necessary patient data for the quantitative synthesis.[8–10,12] No studies were missed because of full-text unavailability, whereas data from the 4 studies that required author contact were successfully received and incorporated in the meta-analysis.

Patient data and study protocols of the included studies comprising a total of 610 patients are summarized in the Table. Risk of bias in the included studies was considered to be moderate, mainly because of the lack of reporting appropriate adjustments for potential confounders in all except for 1 protocol (Table II in the online-only Data Supplement).

In the overall analysis, SP was associated with a reduced risk of MES detection during TCD monitoring compared with patients without SP (risk ratio=0.67; 95% CI, 0.45–0.98), with substantial heterogeneity between studies (I2=52%; Figure 2A). In studies reporting on MES burden, a

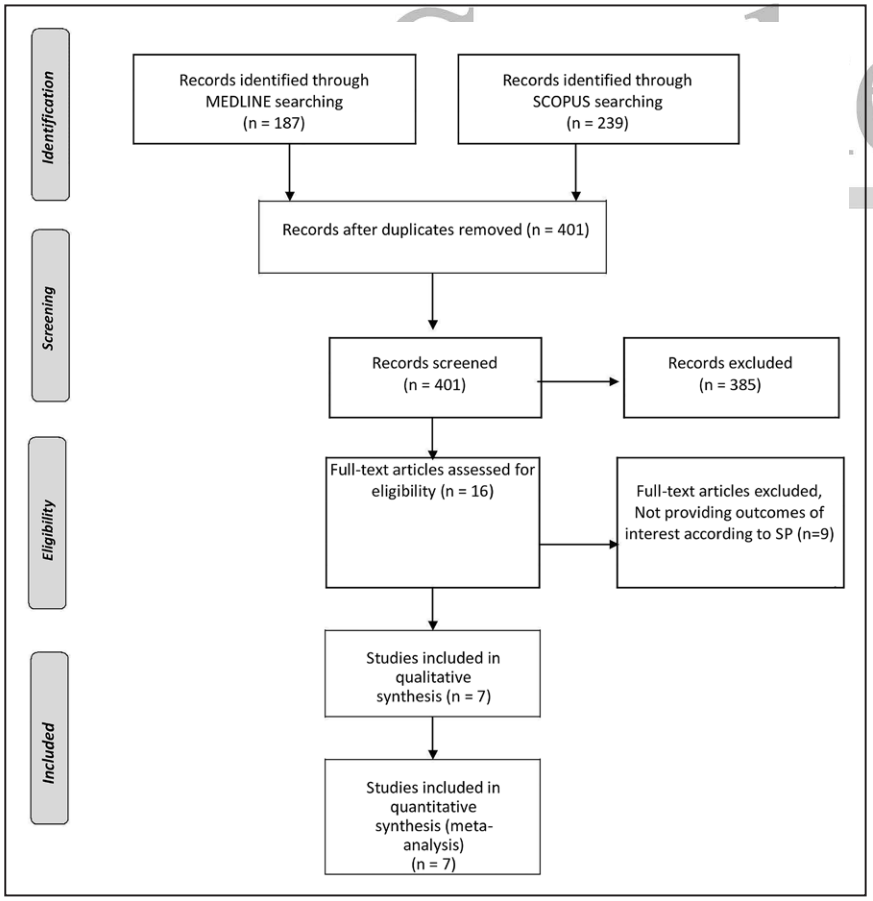

Figure 1. Flowchart is presenting the selection of eligible studies. SP indicates statin pretreatment.

Table. Characteristics of Included Studies

Study Name	Country	N	Age (Mean±SD, y)	Men, %	TIA as Index Event, %	SP, %	APP, %	Symptomatic Vessel Definition	Imaging Method	TCD Monitoring (Duration)	Timing of TCD From Index Event	Insufficient Temporal Window, %*
Choi et al[8]	Canada	64	70±11	89.0	34.4	39.1	N/A	≥50% stenosis or occlusion	CTA	Bilateral (60 min)	≤48 h	10.9
Kerasnoudis et al[9]	Germany	26	70±11	68.7	37.5	50	38.5	>50% stenosis	CDU	Bilateral (30 min)	≤2 wk	N/A
Kinsella et al[10]	Ireland	58	N/A	N/A	N/A	82.7	94.8	≥50% stenosis or occlusion	CDU	Bilateral (60 min)	≤4 wk (early phase); ≥3 mo (late phase)	8.3
Liberman et al[11]	United States	47	66±10	60.0	19	55	51.0	≥50% stenosis or occlusion	N/A	Unilateral (60 min)	≤7 d	25
Müller et al[12]	Switzerland	103	N/A	N/A	22	40.8	100	≥50% stenosis	CDU/CTA	Bilateral (60 min)	≤30 d	6.4
Saedon et al[13]	United Kingdom	206	70±1	72.3	N/A	65.0	72.3	>50% stenosis	CDU	Unilateral (60 min)	≤2 wk	N/A
Safouris et al[4]	Multicenter	106	65±10	72.0	70	40.6	91.5	≥50% stenosis	CTA/MRA	Unilateral (60 min)	≤24 h	N/A

APP indicates antiplatelet pretreatment; CDU, carotid duplex ultrasound; CTA, computed tomography angiography; MRA, magnetic resonance angiography; N/A, not available; SP, statin pretreatment; TCD, transcranial Doppler; and TIA, transient ischemic attack.

*As reported in original publications.

significantly lower number of MES was identified in the SP+ group (mean difference=–0.92; 95% CI, –1.64 to –0.19), with moderate evidence of heterogeneity between studies (I^2=49%; Figure 2B). Funnel plot was found to be asymmetrical (Figure I in the online-only Data Supplement), with a P value for Egger test of 0.076.

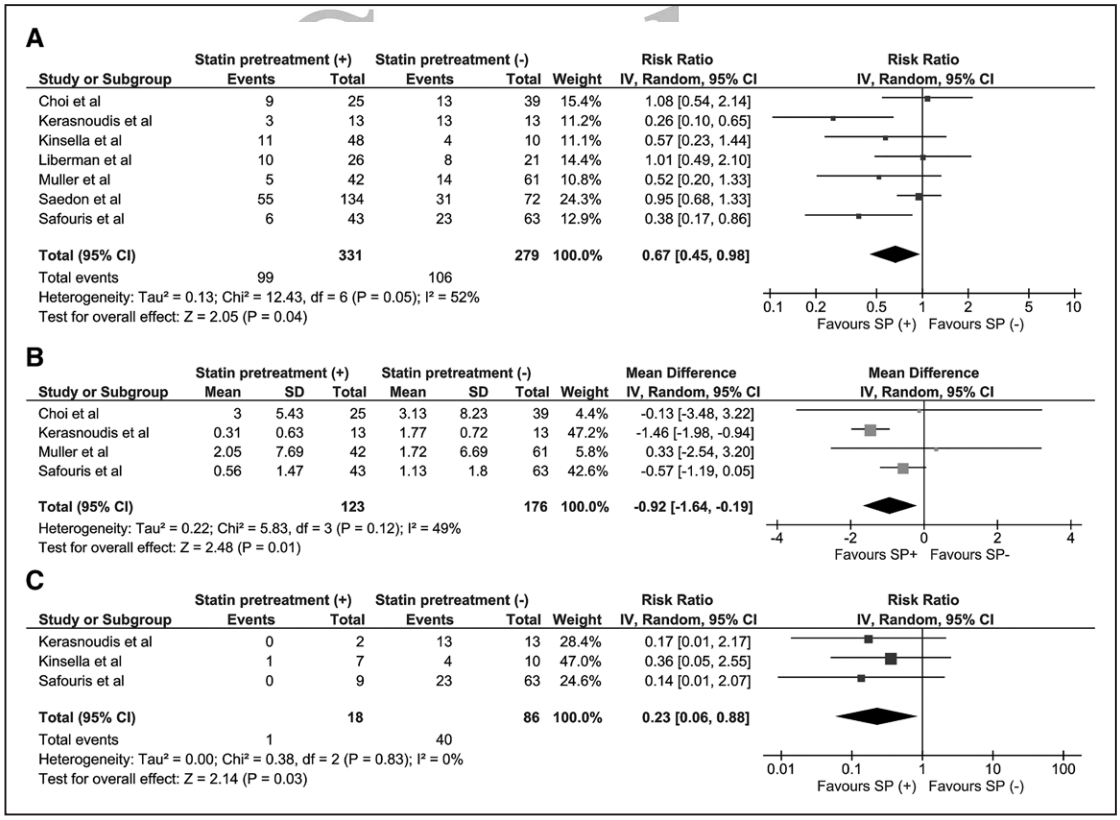

Figure 2. Forest plots of (**A**) the overall analysis of the presence or absence of microembolic signals, (**B**) burden of microembolic signals according to the history of statin pretreatment (SP), and (**C**) subgroup analysis of the presence of microembolic signals in patients with a history of higher-dose statin pretreatment compared with patients without a history of statin pretreatment.

Subgroup analysis revealed that higher-dose SP reduced the risk of detecting MES (risk ratio=0.23; 95% CI, 0.06–0.88) compared with SP− patients, with no evidence of heterogeneity between studies (I^2=0%; Figure 2C).

Discussion

This meta-analysis provides evidence that ACI patients with LAA pretreated with statins have reduced risk of MES presence and lower MES burden on TCD monitoring. Higher-dose SP seems to further reduce the risk of microembolization in real-time compared with no SP.

Our results may partly explain some of the findings of a previous meta-analysis of SP in patients with ischemic stroke, which reported an association of SP with milder initial stroke severity, good functional outcome, and lower mortality.[14] In the same meta-analysis of observational studies, in-hospital statin use was associated with good functional outcome and lower mortality, whereas statin withdrawal after stroke was associated with poor functional outcome. For the time being and for the foreseeable future, we must rely on observational studies about the role of SP in stroke as randomized trials would need a very large presymptomatic study group to achieve statistically significant results. There is still no randomized clinical trial showing a benefit of early statin therapy poststroke and this could be because of small study groups, but it could also be because of the fact that plaque stabilization through statin treatment takes time and the role of statins is more preventive in the long term than neuroprotective in the acute phase. In recent years, there is a trend of clinical guidelines on dyslipidemia to propose more strict goals for cholesterol and higher intensity statin treatment for both primary and secondary ischemic stroke prevention.[15] Our results seem to support this tendency, providing a plausible etiopathogenic hypothesis using real-time TCD monitoring in ACI patients with symptomatic LAA.

Certain limitations of the present meta-analysis need to be acknowledged. All included studies were observational and involved a small number of patients. As a result, there is insufficient data to proceed to other subgroup meta-regression analyses examining antithrombotic treatment or cardiovascular risk factors, and we cannot exclude that some of these confounders may have influenced our results. Moreover, the possibility of publication bias and the presence of small study effect in the present meta-analysis cannot be excluded. Almost all included studies performed TCD monitoring in the anterior circulation, whereas data on the posterior circulation are scarce.

In conclusion, the present meta-analysis indicates that SP is associated with a lower MES incidence and burden in patients with ACI because of LAA. This effect seems to be more pronounced with higher-dose statins.

Disclosures

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SUPPLEMENTAL MATERIAL

Supplemental Methods

Eligible observational study protocols which reported on micro-embolic signal (MES) presence and/or absolute MES number (burden) during transcranial Doppler (TCD) monitoring in patients with symptomatic large vessel stenosis (≥50%) or occlusion stratified by the reported statin pre-treatment (SP) history prior to admission were identified by searching MEDLINE and SCOPUS databases. The detailed search algorithm used on MEDLINE search is outlined below. No language or other restrictions were imposed. Last literature search was conducted on February 23rd, 2018. All retrieved studies were reviewed independently by three authors (AS, AHK & GT), with any disagreement resolved by consensus. We excluded case series, case reports, or studies not reporting any information on SP. In those studies where the original publication reported evidence of SP stratification, but did not contain all necessary data, we contacted the corresponding authors by e-mail.

The systematic search of MEDLINE and SCOPUS databases yielded 187 and 239 results respectively. After removing duplicates, the titles and abstracts of the remaining 401 studies were screened and from the 16 potentially eligible studies 9 studies were excluded for reporting neither MES presence nor burden stratified by SP status (Supplemental Table I).[1-9] In the final evaluation of the literature search results, there was no conflict or disagreement between reviewers and the 7 studies that met the protocol's inclusion criteria were included in the meta-analysis.[10-17]

Complete algorithm used in MEDLINE search

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Fields]) AND ("constriction, pathologic"[MeSH Terms] OR ("constriction"[All Fields] AND "pathologic"[All Fields]) OR "pathologic constriction"[All Fields] OR "stenosis"[All Fields])) OR ("carotid stenosis"[MeSH Terms] OR ("carotid"[All Fields] AND "stenosis"[All Fields]) OR "carotid stenosis"[All Fields] OR ("carotid"[All Fields] AND "artery"[All Fields] AND "stenosis"[All Fields]) OR "carotid artery stenosis"[All Fields]) OR ("vertebrobasilar insufficiency"[MeSH Terms] OR ("vertebrobasilar"[All Fields] AND "insufficiency"[All Fields]) OR "vertebrobasilar insufficiency"[All Fields] OR ("vertebral"[All Fields] AND "artery"[All Fields] AND "stenosis"[All Fields]) OR "vertebral artery stenosis"[All Fields]))) AND ((("ischemia"[MeSH Terms] OR "ischemia"[All Fields] OR "ischemic"[All Fields]) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields])) OR ("cerebral ischaemia"[All Fields] OR "cerebral infarction"[MeSH Terms] OR ("cerebral"[All Fields] AND "infarction"[All Fields]) OR "cerebral infarction"[All Fields] OR ("cerebral"[All Fields] AND "ischemia"[All Fields]) OR "cerebral ischemia"[All Fields] OR "brain ischemia"[MeSH Terms] OR ("brain"[All Fields] AND "ischemia"[All Fields]) OR "brain ischemia"[All Fields] OR ("cerebral"[All Fields] AND "ischemia"[All Fields])) OR ("stroke"[MeSH Terms] OR "stroke"[All Fields]) OR ("transient ischaemic attack"[All Fields] OR "ischemic attack, transient"[MeSH Terms] OR ("ischemic"[All Fields] AND "attack"[All Fields] AND "transient"[All Fields]) OR "transient ischemic attack"[All Fields] OR ("transient"[All Fields] AND "ischemic"[All Fields] AND "attack"[All Fields])))

Supplemental Table I. Excluded studies with reasons for exclusion

Study Name	Reason(s) for exclusion
Altaf et al [1]	Not providing outcomes of interest according to SP
Babikian et al [2]	Not providing outcomes of interest according to SP
Droste et al [3]	Not providing outcomes of interest according to SP
Iguchi et al [4]	Not providing outcomes of interest according to SP
Liu et al [5]	Not providing outcomes of interest according to SP
Orlandi et al [6]	Not providing outcomes of interest according to SP
Sun et al [7]	Not providing outcomes of interest according to SP
Truijman et al [8]	Not providing outcomes of interest according to SP
Wu et al [9]	Not providing outcomes of interest according to SP

SP: statin pretreatment

Supplemental Table II. Quality assessment of included observational studies with the Newcastle–Ottawa Scale [18]

Study name	Selection	Comparability	Outcome	Overall	Comments
Choi et al, 2010 [10]	**		**	4/9	2, 3, 4, 6
Kerasnoudis et al, 2013 [11]	**		**	4/9	2, 3, 4, 6
Kinsella et al, 2015 [12, 13]	***		**	5/9	3, 4
Liberman et al, 2017 [14]	*		**	3/9	1, 2, 4, 6
Muller et al, 2014 [15]	***		**	5/9	3, 4, 6
Saedon et al, 2017 [16]	***	*	**	6/9	3, 5, 6
Safouris et al, 2017 [17]	***	**	**	7/9	3, 6
Overall	17/28	3/14	14/21	34/63	

[1]imaging method for identifying stenosis not reported

[2]consecutivity of included patients not explicitly reported

[3]control cases not selected from community

[4]not adjusting for potential confounders

[5]adjusting for one potential confounder

[6]not reporting the proportion of insufficient temporal windows between cases and controls

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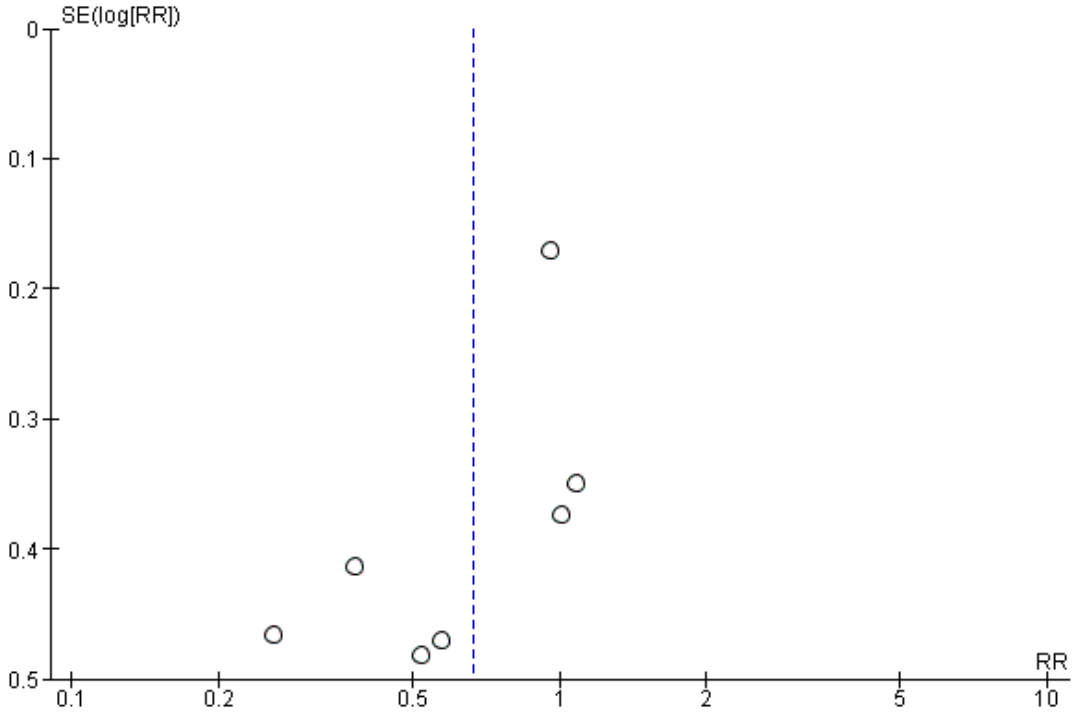
Supplemental Figure I. Funnel plot assessing the risk of potential publication bias



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	p.1 (manuscript)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	p.4 (manuscript)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	p.5 (manuscript)
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	p.5 (manuscript)
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
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.	p.1 (supplement)
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.1 (supplement)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	p.2-3 (supplement)
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.1 (supplement)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	p.1 (supplement)
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.5-6 (manuscript)
Risk of bias in 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.5 (manuscript)

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	p.5-6 (manuscript)
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	p.6 (manuscript)

Section/topic	#	Checklist item	Reported on page #
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.4 (supplement)
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	p.6 (manuscript)
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.	Figure 1 (manuscript)
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.14 (manuscript)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	p.5 (supplement)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2 (manuscript)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	p.7 (manuscript)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	p.7 (manuscript)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	p.7 (manuscript)
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.7 (manuscript)
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).	p.8 (manuscript)

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	p.8 (manuscript)
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.	p.2 (manuscript)

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