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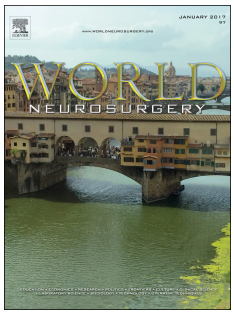

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Minh-Son To, MBiostat, Shivesh Prakash, MD, FCICM, Santosh I. Poonnoose, MCh, FRACS, Shailesh Bihari, MD, PhD, FCICM

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Dose-dependent effects of statins for patients with aneurysmal subarachnoid hemorrhage: meta-regression analysis

Minh-Son To, MBiostat[a]

Shivesh Prakash, MD, FCICM[b,c]

Santosh I Poonnoose, MCh, FRACS[d]

Shailesh Bihari, MD, PhD, FCICM[b,c]

Affiliations

a. School of Medicine, Flinders University, Bedford Park, SA, Australia
b. Department of Intensive and Critical Care Unit, Flinders Medical Centre, Bedford Park, SA, Australia
c. Department of Critical Care Medicine, Flinders University, Bedford Park, SA, Australia
d. Department of Neurosurgery, Flinders Medical Centre, Bedford Park, SA, Australia

Corresponding author

Minh-Son To

Email: minhson.to@gmail.com

Ph: +61 402 649 208

Address for correspondence

Flinders Southern Neurosurgery

Suite 3A – Ground Floor

Bedford Park SA 5042

AUSTRALIA

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AR: absolute risk

ARR: absolute risk reduction

aSAH: aneurysmal subarachnoid hemorrhage

CI: confidence interval

DIND: delayed ischemic neurologic deficit

mRS: modified Rankin Scale

NNT: number needed to treat

RCT: randomized controlled trial

TCD: transcranial Doppler

ABSTRACT

Objective: The study utilizes meta-regression analysis to quantify the dose-dependent effects of statin pharmacotherapy on vasospasm, delayed ischemic neurologic deficits (DINDs) and mortality in aneurysmal subarachnoid hemorrhage (aSAH).

Methods: Prospective, retrospective observational studies and randomized controlled trials (RCTs) were retrieved by a systematic database search. Summary estimates were expressed as absolute risk (AR) for a given statin dose or control (placebo). Meta-regression using inverse variance weighting and robust variance estimation was performed to assess the effect of statin dose on transformed AR in a random effects model. Dose-dependence of predicted AR with 95% confidence interval (CI) was recovered using Miller's Freeman-Tukey inverse.

Results: The database search and study selection criteria yielded 18 studies (2594 patients) for analysis. These included twelve RCTs, four retrospective observational studies and two prospective observational studies. Twelve studies investigated simvastatin, while the remaining studies investigated atorvastatin, pravastatin or pitavastatin, with simvastatin equivalent doses ranging from 20 mg to 80 mg. Meta-regression revealed dose-dependent reductions in Freeman-Tukey transformed absolute risk of vasospasm (slope coefficient -0.00404, 95% CI -0.00720 to -0.00087; p = 0.0321), DINDs (slope coefficient -0.00316, 95% CI -0.00586 to -0.00047; p = 0.0392), and mortality (slope coefficient -0.00345, 95% CI -0.00623 to -0.00067; p = 0.0352).

Conclusions: The present meta-regression provides weak evidence for dose-dependent reductions in vasospasm, DINDs and mortality associated with acute statin use following aSAH. However, the analysis was limited by substantial heterogeneity among individual studies. Higher dosing strategies are a potential consideration for future RCTs.

INTRODUCTION

Subarachnoid hemorrhages account for 3% of all strokes[1, 2] and despite improvements in outcomes case mortality rates still approach 50%[3]. Intracranial aneurysm rupture is the cause of 85% of subarachnoid hemorrhages and is nowadays managed with surgical clipping or endovascular coiling of the aneurysm to prevent re-rupture and further bleeding. After the initial bleed, vasospasm and delayed ischemic neurological deficits (DINDs) are significant contributors to long-term morbidity and mortality. Angiographic evidence of vasospasm may be demonstrated in up to two-thirds of aneurysmal SAH (aSAH) patients[4]. Vasospasm following aSAH typically occurs between 4 to 14 days after ictus, resolving by 21 days. Vasospasm is also associated with and may contribute to symptomatic delayed ischemic neurological deficit (DIND), which is seen in approximately one third of patients. While various pharmacological approaches for preventing vasospasm and DIND have been explored[5], nimodipine remains the only pharmacological intervention that has been shown to reduce vasospasm and DIND after SAH[6-8].

Statin therapy is another intervention that has received significant attention but their role in aSAH remains uncertain. Experimental animal models have shown reduction of cerebral vasospasm after aSAH with simvastatin[9, 10]. Beyond their lipid lowering effects, it is thought that the neuroprotective advantages of statins in aSAH arise from their pleiotropic effects. These include anti-platelet[11], anti-oxidative[12] and anti-inflammatory effects[13]. Statins also produce cerebral vasodilation by increasing endothelial-derived nitric oxide synthase activity[14].

However, these experimental findings have only been reproduced in human aSAH studies with limited success. In a single-institution prospective observational cohort study, McGirt et al.[15] compared 170 consecutive patients treated with 80 mg simvastatin against 170 consecutive patients in the pre-statin era found no difference in incidence of symptomatic vasospasm (25.3% vs 30.5%; $p = 0.277$) or in-hospital mortality (18% vs 15%; $p = 0.468$). This study was followed by the

large multicenter STASH randomized trial[16], which included 803 patients randomly assigned to receive either 40 mg simvastatin (n = 391) or placebo (n = 412). In the STASH trial, there was also no significant reduction of clinical delayed ischemic deficits (64/391 vs 67/412; p = 0.9675) or in-hospital mortality (34/391 vs 33/412; no p-value given). More recently, Wong et al.[17] in a randomized trial of 255 patients, compared 80 mg simvastatin against 40 mg simvastatin daily for three weeks and found no difference in the incidence of delayed ischemic deficits (27% vs 24%; p = 0.586) among the two treatment levels. In contrast to these three studies, a retrospective case control study of 278 patients by Sanchez-Peña et al.[18] considered the impact of 40 mg oral atorvastatin post-aSAH and concluded atorvastatin reduced the incidence of vasospasm compared to control (41/136 vs 61/142; p = 0.027). These studies been interspersed by several smaller studies that have demonstrated positive effects of statins. For example, Tseng et al.[19] in a randomized trial of 80 aSAH patients showed a 32% reduction (p = 0.006) in incidence of vasospasm associated with pravastatin therapy while another contemporaneous randomized trial of 39 aSAH patients also showed significant reduction in vasospasm in the simvastatin group[20].

Multiple meta-analyses have also investigated the potential benefit of statins in aSAH but have reached differing conclusions[21-27]. Two important issues commonly encountered when comparing the original studies are the variable choice of statin therapy as well as different dosing strategies implemented. While most studies have investigated simvastatin, others have also considered pravastatin and atorvastatin. Likewise, a range of doses have been investigated e.g. simvastatin from 20 mg up to 80 mg. If not handled appropriately, such heterogeneity may obscure a potential benefit of statins that is only seen at higher doses. One recent meta-analysis has attempted to account for heterogeneity in dosing by performing subgroup analyses with stratification by statin dose[22], and suggested that a reduction in DINDs and mortality was only seen with high-dose subgroup. As statin dose is quantifiable, an alternative approach is to perform meta-regression analysis. By estimating the linear relationship between dose and specified outcomes, meta-regression is therefore a suitable approach to account for dose-related heterogeneity[28] and addressing whether a dose-dependency exists. In the present study, we perform such a meta-

regression analysis of randomized and observational studies to investigate whether statin therapy is associated with a dose-dependent change in angiographic vasospasm, DINDs or mortality following aSAH. Using the estimated meta-regression linear models, we also predict the dose-effect relationships of statin therapy on these outcomes.

METHODS

Search strategy and study selection

Articles were searched in Scopus, PubMed and the Cochrane Central Register of Controlled Trials. Search terms included “simvastatin”, “pravastatin”, “atorvastatin”, “statin”, “statins”, “aneurysmal subarachnoid hemorrhage”, “aneurysmal subarachnoid hemorrhage”, “vasospasm”, “DIND” and “mortality”. Citations and citing articles of the retrieved articles were also screened to identify additional relevant studies. Conference abstracts were included in the search. There were no language restrictions and studies not in English were translated to English. Articles were last searched on the 14th of August 2017.

Inclusion criteria were (1) randomized control trials (RCTs), prospective or retrospective observational studies that investigated the effect of statins in aneurysmal subarachnoid hemorrhage; (2) study endpoints included at least one of cerebral vasospasm, DIND or mortality. Exclusion criteria were (1) studies that investigated the effect of statins in animals; (2) non-aneurysmal SAH e.g. trauma or arteriovenous malformation rupture; (3) studies investigating the effect of long-term statin use, statin treatment investigated prior to SAH.

Data extraction and analysis

The literature search and data extraction were performed independently by two reviewers (M-ST, S Prakash) according to pre-determined study selection criteria. Disagreements were resolved by involvement of a third author (SB). Quality assessment of the selected studies was performed using the risk of bias tool provided by the Cochrane Collaboration[29]. The following data were extracted: first author, year of publication, study design, study size, patient characteristics, subarachnoid grading, intervention characteristics and outcomes.

Outcomes extracted were vasospasm, DIND and mortality. We required angiographic evidence or flow measurements for inclusion of vasospasm data. Absolute risks (ARs) were extracted from the number of outcome events in each treatment group. Non-simvastatin therapy doses were converted to simvastatin-equivalent doses (Table 1)[30], while placebo or no treatment was assigned a simvastatin-equivalent dose of 0 mg. Outcomes were expressed as absolute risk (AR) for a given statin dose or control (placebo). Individual study ARs were transformed using Freeman-Tukey arcsine square root transformation $x \rightarrow \sin^{-1}\sqrt{\frac{x}{n+1}} + \sin^{-1}\sqrt{\frac{x+1}{n+1}}$. Meta-regression using inverse variance weighting and robust variance estimation[31] with small sample adjustment[32] was performed to assess the effect of statin dose on transformed AR in a random effects model. The sign of the estimated slope coefficients was used to detect a dose-dependent relationship between transformed AR and statin dose. Sensitivity analysis of the estimated slope coefficients was performed by removing single studies at a time. The dose-dependence of predicted AR with 95% confidence interval (CI) was recovered using Miller's Freeman-Tukey inverse $x \rightarrow \frac{1}{2}\left\{1 - |\cos x|\left[1 - \left(\sin x + \left(\sin x - \frac{1}{\sin x}\right)/n\right)^2\right]^{1/2}\right\}$ [33]. Tests for the regression coefficients were two-sided with a significance level of 0.05. All statistical analyses were performed using Stata/IC 14 (Stata Corp, College Station, TX, USA)[34].

Predicted absolute risk, number needed to treat and study size calculations

The linear model obtained from meta-regression also allows estimation of absolute risk using the Freeman-Tukey inverse. The absolute risk reduction (ARR) can then be calculated as $ARR = p_0 - p_s$, where p_0 and p_s denote the absolute risk at baseline and with a given dose of statin therapy, respectively. The number needed to treat (NNT) is therefore $NNT = 1/ARR$. Finally, the number required per group to detect a difference in these estimated absolute risks with power $(1 - \beta)$ and a two-sided significance level α is given by[35]:

$$n = \left[\frac{Z_{1-\propto/2}\sqrt{2\bar{p}\bar{q}} + Z_{1-\beta}\sqrt{p_0(1-p_0) + p_s(1-p_s)}}{(p_0 - p_s)}\right]^2,$$

where $\bar{p} = \frac{p_0+p_s}{2}$ and $\bar{q} = 1 - \bar{p}$. With a significance level $\alpha = 0.05$ and power $1 - \beta = 0.8$, we have $Z_{1-\propto/2} = 1.96$ and $Z_{1-\beta} = 0.842$.

RESULTS

Search results

The literature search strategy yielded a total of 18 studies for analysis, which comprised of randomized controlled trials (RCTs)[16, 17, 19, 20, 36-43], prospective observational cohort studies[15, 44] and retrospective observational studies[18, 45-47]. This represented 2594 patients. Two studies were published as abstracts[37, 39]. One study published in Chinese was translated into English[42]. Four studies were excluded for their focus on the effect of pre-SAH statin use on outcomes[48-51]. The selection of studies is shown in Figure 1A. The quality of the included studies was measured by the Cochrane risk of bias assessment tool[29] (Figure 1B). If bias was not addressed in the trials, we assumed an unclear risk. Nine studies (50.0%) were randomized control trials, with blinding of participants and personnel[16, 17, 19, 20, 36, 38, 40, 41, 43]. Risk of overall bias was considered high in 7 studies (39.0%)[15, 37, 39, 42, 44-46], whereas the risk was minimal in 8 studies (44.4%)[16, 17, 19, 20, 36, 38, 40, 41].

Characteristics of eligible studies and study interventions

Characteristics of patients from included studies are shown in Table 2. The majority of patients were female and most underwent surgical clipping or endovascular coiling after presentation. Garg et al.[40] included clipped patients only. Clinical severity of aSAH was graded using the WFNS scale in 10 studies; 27.9% (443/1585) of patients were WFNS grade 4 or higher. Several studies also reported Hunt-Hess grade (not shown). Fisher grade was reported in 12 studies; among these 40.6% (884/2179) patients were grade 4.

Definitions of study outcomes (vasospasm, DIND, mortality) are shown in Table 3 and characteristics of study interventions are shown in Table 4. Of the 18 studies, twelve investigated simvastatin[15-17, 20, 36, 38-41, 44, 46, 47], three investigated pravastatin[19, 37, 45] two investigated atorvastatin[18, 42] while a single study investigated pitavastatin[43]. Simvastatin dose ranged from 20 mg to 80 mg daily and atorvastatin ranged from 20 mg to 40 mg daily. Only 40 mg of pravastatin daily and 4 mg of pitavastatin daily were investigated. Two studies did not include a control/placebo group[17, 44], one of which included three statin treatment groups[44]. One study involved a simvastatin and magnesium treatment arm[46], but this arm was excluded from analysis. Duration of statin treatment varied but generally did not exceed 21 days except in[16].

Detection of vasospasm relied on transcranial Doppler (TCD) flow measurements in most studies, most commonly of the middle cerebral artery (MCA), however different criteria were used including maximal or mean flows. The Lindegaard ratio (MCA mean blood flow velocity/extracranial internal carotid artery mean blood flow velocity) was utilized in four studies. Angiographic vasospasm was not reported in five studies. DIND was reported in all studies except one. Observation of DIND was largely clinical. Most studies required a deterioration in Glasgow Coma Score (GCS) of at least two points or change in neurological status not attributable to another cause. Mortality was reported in all but three studies. Again, the definition of mortality varied between the studies, ranging from in-hospital mortality to mortality at six months follow-up.

Meta-regression analysis of study outcomes

We utilized a meta-regression approach to quantify the relationship between aSAH outcomes (Table 4) and statin dose (Table 5 and Figure 2). As the Freeman-Tukey arcsine square root transformation is nonlinear, the estimated regression coefficients only represent the linear relationship for the transformed outcome covariate and dose, whereas the relationship between AR and dose is nonlinear after inverse transformation. Applying the Freeman-Tukey transform on the proportions of vasospasm and fitting the linear regression on the transformed variable showed that higher doses of simvastatin were associated with a lower incidence of vasospasm ($p = 0.032$). Similarly, increasing simvastatin dose was also associated with reduced rates of DIND ($p = 0.039$) and mortality ($p = 0.035$). However, sensitivity analysis showed that these meta-regression outcomes were not strongly robust to exclusion of individual studies. Individual exclusion of 6 out of 13 studies led to statistically non-significant coefficients for the vasospasm outcome. For DIND this figure was 7 out of 17 studies, and for mortality 7 out of 14 studies.

The regression model can be used to predict the dose-dependent AR of the various outcomes (Table 6). Inverting the transformed linear regression yields a predicted AR of vasospasm of 43.4% (95% CI; 35.8% to 51.1%) at 0 mg simvastatin compared to 26.3% (95% CI; 13.8% to 40.9%) at 80 mg. Likewise, the predicted AR of DIND of 33.8% (95% CI; 24.7% to 44.4%) at 0 mg simvastatin compares to 20.6% (95% CI; 13.4% to 28.7%) at 80 mg. Finally, there is a predicted AR of mortality of 16.8% (95% CI; 11.9% to 22.1%) at 0 mg simvastatin compared to 8.4% (95% CI; 3.3% to 15.2%) at 80 mg. The predicted AR values can then be used to derive predicted ARR and NNT. These are shown in Table 6. Finally, the predicted AR can be used to estimate the minimum sample sizes required to detect reductions in AR at a significance level of $\alpha = 0.05$ (two-sided) and power $1 - \beta = 0.8$ (Table 6; see also Methods).

DISCUSSION

The present study provides some evidence that statin therapy is associated with dose-dependent reductions in incidence of vasospasm, DIND and mortality following aSAH. Meta-regression analysis of Freeman-Tukey transformed proportions does not provide a linear relationship between risk of outcome and dose since the transformation is nonlinear. Instead the absolute risk at different doses can be estimated post-regression by inverting the transformation on the prediction model produced by regression. This approach yielded significant estimated ARR in vasospasm, DIND and mortality of 16.4%, 11.6% and 9.5%, respectively, with corresponding NNT of 7, 9 and 11. However, sensitivity analysis showed that these findings were not robust to exclusion of individual studies and may reflect a high degree of heterogeneity among the studies.

These results need to be taken in context of the findings of previous studies. The studies by Sanchez-Peña et al.[18] and Li[42] were the only in our analysis that considered atorvastatin and found a positive benefit on the incidence of vasospasm. Whether this benefit was specific to atorvastatin or reflects a class effect of statins remains unclear. Our results are also at odds with several studies that have not demonstrated significant improvements in outcomes with statin therapy. One explanation is that many studies may not have been sufficiently powered to reliably detect a difference in outcomes. Related to this, trials that have only utilized a relatively low dose of statin may not have produced a detectable difference in outcome. For example, the largest randomized trial to date, the STASH trial[16], included 803 patients randomized to 40 mg simvastatin treatment with modified Rankin Scale (mRS) at 6 months as the primary outcome. Mortality is included in this scale. In Table 6 we include sample size calculations based on dose-dependent predicted absolute risks. At a simvastatin dose of 40 mg, we note that a substantially larger study size of 1830 would be required to detect a reduction in mortality with 80% power. Furthermore, this dosing level is in the lower range of therapy available.

A number of recent meta-analyses have broached the subject of whether statins may be beneficial in aSAH but have reached differing conclusions[21-27]. Our sensitivity analysis provides some insight into the discrepancies since statistical significance of the meta-regression coefficients was sensitive to exclusion of individual studies. The variations in study selection criteria across individual meta-analyses is likely to contribute to the lack of consensus among previous meta-analyses.

Our study has several limitations. Our dose equivalence conversion was based on the known cholesterol-lowering effects of statins. Whether the same dose conversion applies to their pleiotropic effects is less clear. There is some evidence however that this may be the case[52]. However, all statins are not created equal and this element is not incorporated into the analysis. On the one hand, simvastatin and pravastatin have superior safety and tolerability profiles[53]; on the other, simvastatin, atorvastatin and pitavastatin are lipophilic and thus should cross the blood-brain barrier to similar extents whereas pravastatin is hydrophilic[54]. Brain metabolism of statins has not been studied and it is unclear whether the acid or lactone forms exert neuroprotective effects in the brain[50]. We did not analyze the rate of side effects associated with statin therapy, since we found this information to be inconsistently reported. Outcomes were analyzed as absolute risk instead of relative risk for several reasons. While relative risk measures may be more consistent[55, 56], they are relative and require measurement of absolute risk at some baseline, typically placebo or the no-dose scenario. In contrast, absolute risk is directly related to incidence and importantly, absolute risk measures enabled inclusion of studies that were not placebo controlled[17, 44]. Utilization of absolute risk and absolute risk reduction also allowed derivation of indices such as number needed to treat (Table 6).

We also observed substantial heterogeneity across the studies. This was partly reflected in our sensitivity analysis. While we attempted to account for one source, namely dose of statin, we can identify several other important sources of heterogeneity that are more difficult to account for by meta-regression. These include choice of statin and duration of treatment, since in some studies, duration was variable. Heterogeneity may also arise from the inclusion of RCTs as well as

prospective and retrospective observational studies. Randomized controlled studies typically impose stricter inclusion criteria and consequently may exclude the most ill patients who, at the same time, would also derive the greatest benefit from therapy. For example, Garg et al. excluded Hunt and Hess Grade V aSAH[40] and thus their findings may not generalize to all aSAH patients. Conversely, exclusion criteria may also limit patients with comorbidities such as hepatic, renal or other systemic disease, and it is these patients who are also more vulnerable to side effects of therapy. Taken together, it can be argued that observational studies include patients more representative of the typical population at risk[57].

Definitions of DIND varied across studies as did criteria for establishing the presence of vasospasm. Many of the studies required a new onset reduction in GCS, while some also relied on radiologic evidence of ischemia to confirm DIND. TCD was a widely-adopted modality for confirming vasospasm, but velocity thresholds differed between studies as well as whether peak or mean velocities were utilized. In contrast, mortality was simpler to establish, but follow-up duration varied; mortality “at discharge” was frequently but not universally adopted. These differences may arise from institution-specific practices or resource limitations. Moreover, such inconsistencies present challenges to comparing studies by contributing to heterogeneity. We therefore highlight a need to establish uniform definitions of these outcomes to enable direct comparisons of future studies and evaluate the efficacy of interventions more effectively. One such definition for delayed ischemia has been proposed[58].

Meta-regression analysis is hypothesis generating and provides some guidance on future studies and appropriate dosing strategies. The adverse effects of high-dose strategies must be weighed against the potential benefits of statin therapy on the devastating sequelae of aSAH. However, the side effects profile of statins is well-known and has been extensively explored[53, 59]. Importantly, even high-dose 80 mg atorvastatin daily is only associated with a relatively low risk of serious hepatic or musculoskeletal adverse effects (0.6% and 1.3%, respectively)[60, 61]. These features

are advantageous in the design of studies and may enable anticipation or mitigation of potential adverse effects.

CONCLUSIONS

Statin therapy is associated with dose-dependent reductions in incidence of vasospasm, DIND and mortality following aSAH. We do not recommend changing current practice on the basis of our meta-regression analysis. On the other hand, these results provide guidance for the design of future studies and support further exploration of high-dose strategies.

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Figure 1: Study identification and risk of bias. (A) PRISMA flow diagram showing steps to selection of relevant studies for meta-regression analysis. (B) Risk of bias assessment. Shading represents degree of bias (green, low risk; yellow, unclear risk; red, high risk).

Figure 2: Meta-regression analysis of the effect of statin dose on outcomes. Outcomes shown are vasospasm (A,B; green), DIND (C,D; red) and mortality (E,F; blue). (A,C,E) Meta-regression of individual studies (grey lines) produces a linear estimate of the Freeman-Tukey transformed risk of outcome versus dose relationship (colored line). (B,D,F) The estimated linear estimates were inverted to provide the absolute risk of outcome at different statin doses (colored line). Individual intervention groups are shown (black dots). Grey shading indicates 95% confidence interval of the estimates.

Both Figures are for color in print

Table 1 – Simvastatin equivalent dosing

Simvastatin	Pravastatin	Atorvastatin	Pitavastatin
10 mg	20 mg	-	1 mg
20 mg	40 mg	10 mg	2 mg
40 mg	80 mg	20 mg	4 mg
80 mg	-	40 mg	8 mg

Table 2 – Study and patient characteristics

Study, year	Study design	Study size	Mean age, years ± SD (range)	Female (%)	WFNS ≥ 4	Fisher grade ≥ 4	Clip	Coil
Lynch et al, 2005[20]	RCT	39	56 ± 15	33 (85)	-	2	17	22
Tseng et al, 2005[19]	RCT	80	53 ± 12	44 (55)	26	-	52	13
Chou et al, 2008[36]	RCT	39	53 ± 13	29 (75)	-	0	33	6
Jaschinski et al, 2008[37]	RCT	98	-	-	-	-	42	24
Kerz et al, 2008[46]	ROS	72	55 (47 – 64)	43 (60)	24	46	18	20
Kramer et al, 2008[47]	ROS	150	55 (53 – 59)	104 (69)	48	46	80	65
Kern et al, 2009[45]	ROS	130	56 ± 14	64 (49)	33	46	50	67
McGirt et al, 2009[15]	POS	340	53 ± 13	256 (75)	-	125	175	65
Vergouwen et al, 2009[38]	RCT	32	53 ± 11	20 (63)	8	-	7	24
Li, 2010[42]	RCT	47	-	21 (45)	-	-	-	-
Macedo et al, 2010[39]	RCT	20	-	-	-	-	-	-
Sanchez-Peña et al, 2012[18]	ROS	278	53 ± 14	178 (64)	-	79	47	231
Garg et al, 2013[40]	RCT	38	49 ± 9	17 (45)	1	0	38	0
Kirkpatrick et al, 2014[16]	RCT	803	50 ± 10	551 (69)	184	406	254	513
Wong et al, 2015[17]	RCT	255	57 ± 10	165 (65)	109	73	133	101
Woo et al, 2015[44]	POS	87	55 ± 12	62 (71)	-	54	61	26
Diringer et al, 2016[41]	RCT	25	60 ± 11	16 (64)	10	7	-	-
Naraoka et al, 2017[43]	RCT	108	58 ± 11	74 (69)	-	-	99	9

POS, prospective observational study; ROS, retrospective observational study; RCT, randomized control study; SD, standard deviation; WFNS, World Federation of Neurosurgical Societies

Table 3 – Study outcome definitions

Study, year	Vasospasm	DIND	Mortality
Lynch et al, 2005[20]	Angiographic or TCD (V_{MCA} > 160 m/s) in conjunction with DIND	Clinical impression of DIND (unrelated to rebleed, hydrocephalus, or infection) with confirmatory radiography	Not defined
Tseng et al, 2005[19]	TCD (V_{MCA} > 120 cm/s, LR > 3)	Development of focal neurological deficits or drop in GCS ≥ 2 points	At discharge
Chou et al, 2008[36]	TCD (peak systolic MCA flow velocity > 200 cm/s, LR > 3); 23 (59%)	Drop in modified GCS ≥ 2 points or unaccountable new focal neurological deficit lasting ≥ 2 hours	At discharge
Jaschinski et al, 2008[37]	-	Not defined	ICU mortality
Kerz et al, 2008[46]	-	Drop in GCS ≥ 2 points, new focal deficit or TCD mean flow velocity of > 120 cm/s or increase > 50 cm/s on 2 consecutive days	14 day in-hospital mortality
Kramer et al, 2008[47]	Radiographic vasospasm (> 33% narrowing) on CT or catheter angiography	Change in neurological status not attributable to another cause (e.g. seizure, hydrocephalus, recent sedation, or metabolic derangement) with at least moderate radiographic vasospasm	At discharge or 6-week follow-up
Kern et al, 2009[45]	TCD (V_{MCA} > 120 cm/s, LR > 3)	Focal neurological deficits not explained by hydrocephalus, surgical trauma, or new hemorrhage	In-hospital mortality
McGirt et al, 2009[15]	-	Change in neurological status not attributable to another cause (e.g. seizures, hydrocephalus, recent sedation, repeat hemorrhage, clip-induced infarct, or metabolic derangement)	Death within 28 days of admission
Vergouwen et al, 2009[38]	TCD (V_{MCA} or V_{ACA} ≥ 120 cm/sec)	Gradual deterioration with focal neurologic impairment and/or a drop in GCS ≥ 2 points	Death on GOS at 3 months
Li, 2010[42]	TCD (V_{MCA} > 120 cm/s)	Vasospasm together with delayed neurological impairment not due to another cause (e.g. bleeding, intracerebral hematoma or hydrocephalus)	-
Macedo et al, 2010[39]	Cerebral arteriography	Altered neurological signals in presence of changes suggestive of vasospasm or correlation in clinical and CT scans	Not defined
Sanchez-Peña et al, 2012[18]	Vessels assessed on angiogram showing the most severe abnormalities	-	-
Garg et al, 2013[40]	TCD (maximal MCA velocity ≥ 160 cm/sec at any point of time within 14 days)	New ischemic neurological deficits in 1st 2 weeks after ictus not attributable to other causes	Not defined
Kirkpatrick et al, 2014[16]	-	Deterioration in GCS ≥ 2 points not be attributable to any other cause including sepsis	Mortality at 6 months
Wong et al, 2015[17]	-	Drop in GCS ≥ 2 points or new focal neurological deficit last more than 2 hours	Death on mRS at 3 months
Woo et al, 2015[44]	TCD (highest V_{MCA} > 150 cm/s in single test, change in highest V_{MCA} > 50 cm/s in serial test, or LR > 3)	Drop in GCS ≥ 2 points and clinical deterioration	-

Diringer et al, 2016[41]	Angiography, moderate or severe vasospasm of distal segments of the ACA, MCA, and PCA	New focal deficit or global decline in consciousness after exclusion of other causes of neurological deterioration	Death on mRS at 6 months
Naraoka et al, 2017[43]	Angiographic (DSA), ≥ 25% decrease in arterial wall diameter compared to baseline DSA	New focal, neurological deficits or drop in GCS ≥ 2 points	-

CT, Computed tomography; DSA, Digital subtraction angiography; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Score, LR; Lindegaard ratio (middle cerebral artery mean blood flow velocity/extracranial internal carotid artery mean blood flow velocity); mRS, modified Rankin Scale; TCD, transcranial Doppler; ACA, anterior cerebral artery; MCA, middle cerebral artery; $V_{MCA/ACA}$, MCA/ACA mean flow velocity

Table 4 – Study interventions and outcomes by simvastatin equivalent dose

Study, year	Statin	Dose (simvastatin equivalent; mg)	Group size	Duration of treatment	Vasospasm, n	DIND, n	Mortality, n
Lynch et al, 2005[20]	S	CTL 80	20 19	Simvastatin for 14 days	12 5	12 5	3 0
Tseng et al, 2005[19]	P	CTL 40	40 40	Up to 14 days	25 17	12 2	8 2
Chou et al, 2008[36]	S	CTL 80	20 19	Maximum of 21 days or until discharge	10 13	10 7	3 0
Jaschinski et al, 2008[37]	P	CTL 40	58 40	-	-	35 13	13 9
Kerz et al, 2008[46]	S	CTL 40	51 21	14 days	-	8 5	14 7
Kramer et al, 2008[47]	S	CTL 80	71 79	14 days	33 29	20 23	8 11
Kern et al, 2009[45]	P	CTL 40	58 72	14 days	24 30	25 29	8 15
McGirt et al, 2009[15]	S	CTL 80	170 170	At least 14 days	-	52 43	26 31
Vergouwen et al, 2009[38]	S	CTL 80	16 16	15 days	11 12	5 6	2 2
Li, 2010[42]	A	CTL 20	23 24	14 days	13 6	7 2	-
Macedo et al, 2010[39]	S	CTL 80	9 11	21 days	4 1	5 1	6 2
Sanchez-Peña et al, 2012[18]	A	CTL 40	136 142	At least 14 days	47 32	-	-
Garg et al, 2013[40]	S	CTL 80	19 19	14 days	5 3	8 5	3 1
Kirkpatrick et al, 2014[16]	S	CTL 40	412 391	21 days or until discharge	-	67 64	35 37
Wong et al, 2015[17]	S	40 80	131 124	21 days	-	32 34	7 6
Woo et al, 2015[44]	S	20 40 80	22 34 31	Simvastatin for 14 days	6 4 4	8 3 1	--
Diringer et al, 2016[41]	S	CTL 80	12 13	Up to 14 days	5 5	7 2	2 0
Naraoka et al, 2017[43]	Pi	CTL 40	20 19	14 days	34 24	12 7	-

A, atorvastatin; Pi, pitavastatin; P, pravastatin; S, simvastatin; CTL, control/placebo

Table 5 – Meta-regression coefficients

Transformed outcome	Number of studies	Number of patients	Coefficient	SE	95% CI	p-value
Vasospasm	13	1171	-0.00404	0.00162	(-0.00720, -0.00087)	0.0321
DIND	17	2363	-0.00316	0.00138	(-0.00586, -0.00047)	0.0392
Mortality	14	2229	-0.00345	0.00142	(-0.00623, -0.00067)	0.0352

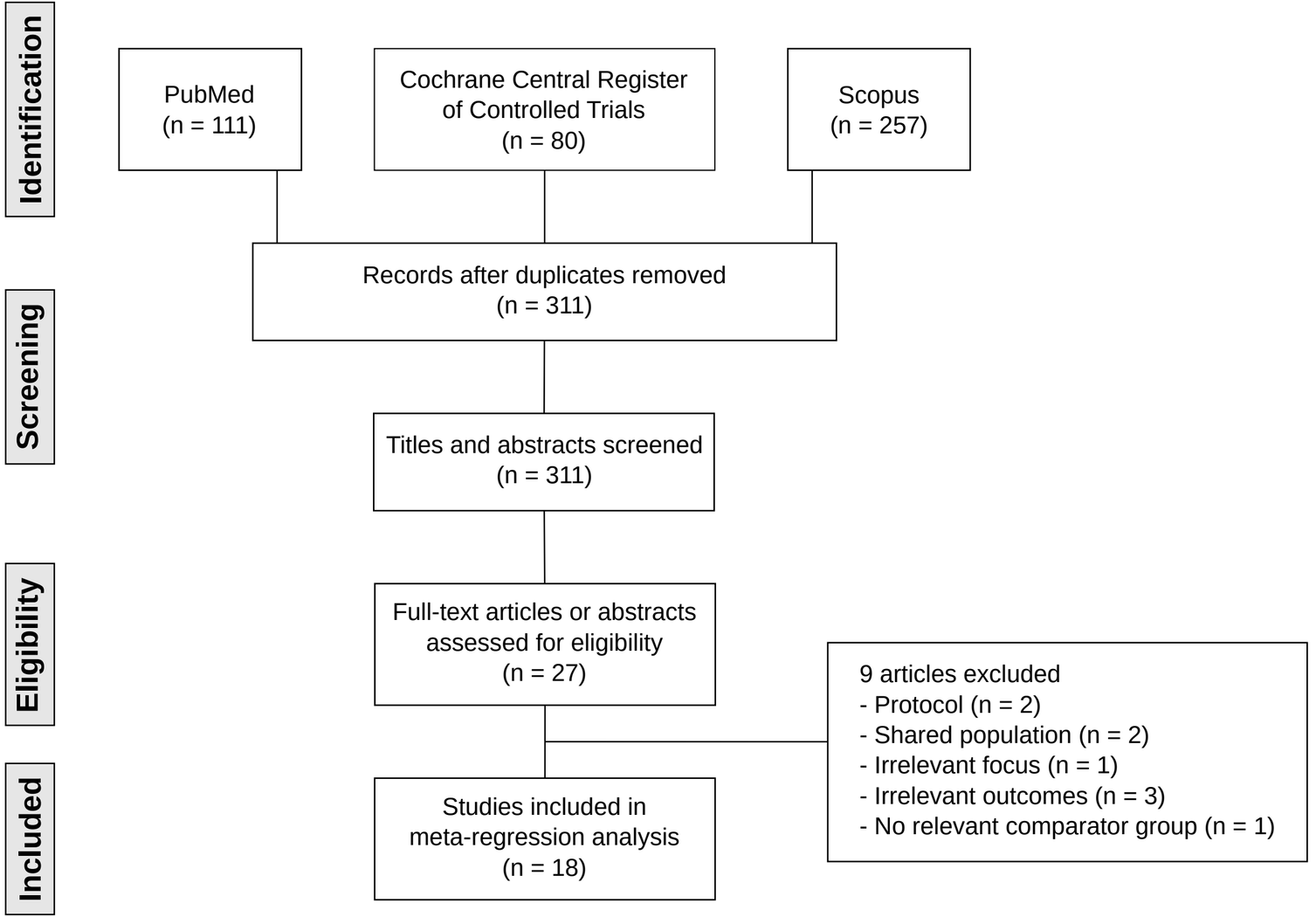
SE, standard error; CI, confidence interval

Table 6 – Predicted absolute risk of adverse outcomes associated with statins

Outcome	Dose	AR	95% CI	ARR	NNT	Study size
Vasospasm	0 mg	47.2%	40.1% to 54.4%	-	-	-
	20 mg	43.0%	35.5% to 50.8%	4.2%	24	6872
	40 mg	38.9%	29.6% to 48.6%	8.3%	13	1380
	80 mg	30.9%	17.3% to 46.2%	16.4%	7	360
DIND	0 mg	32.0%	23.3% to 41.3%	-	-	-
	20 mg	28.9%	22.2% to 36.1%	3.0%	33	8902
	40 mg	26.0%	20.4% to 32.0%	6.0%	17	2254
	80 mg	20.4%	14.1% to 27.4%	11.6%	9	580
Mortality	0 mg	16.6%	11.4% to 22.5%	-	-	-
	20 mg	14.0%	9.9% to 18.6%	2.6%	38	7211
	40 mg	11.5%	7.5% to 16.1%	5.1%	20	1830
	80 mg	7.1%	2.3% to 13.9%	9.5%	11	482

AR, absolute risk; CI, confidence interval; NNT, number needed to treat

A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Scopus
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Records after duplicates removed
(n = 311)
Titles and abstracts screened
(n = 311)
Full-text articles or abstracts
assessed for eligibility
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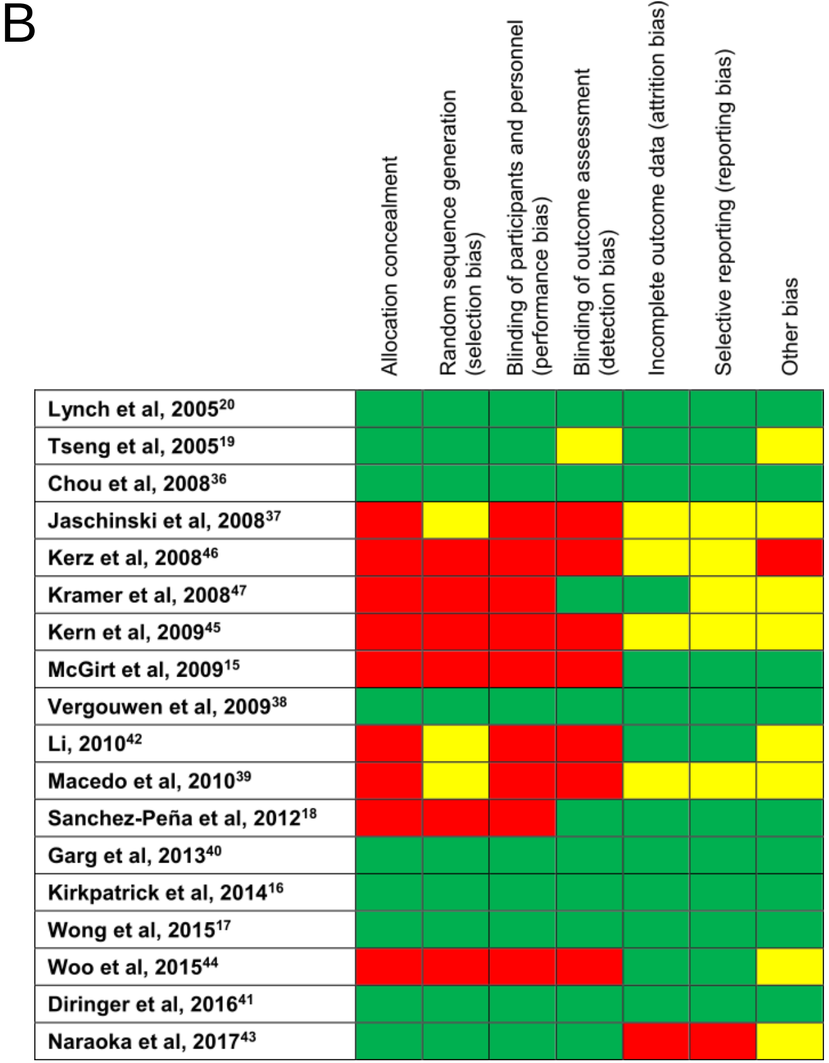
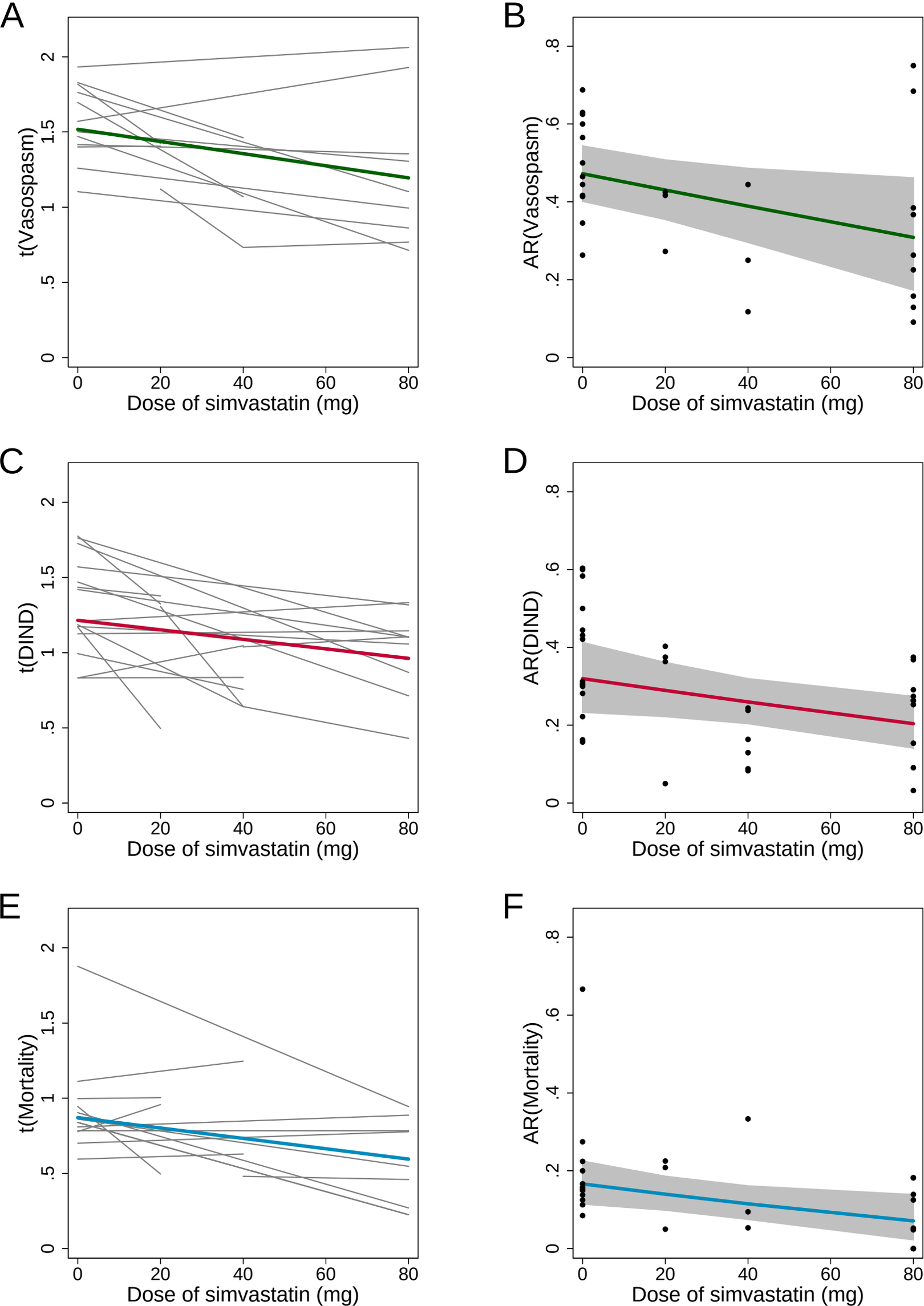
9 articles excluded
- Protocol (n = 2)
- Shared population (n = 2)
- Irrelevant focus (n = 1)
- Irrelevant outcomes (n = 3)
- No relevant comparator group (n = 1)
Studies included in
meta-regression analysis
(n = 18)

B


Allocation concealment
Random sequence generation (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
Lynch et al, 2005[20]
Tseng et al, 2005[19]
Chou et al, 2008[36]
Jaschinski et al, 2008[37]
Kerz et al, 2008[46]
Kramer et al, 2008[47]
Kern et al, 2009[45]
McGirt et al, 2009[15]
Vergouwen et al, 2009[38]
Li, 2010[42]
Macedo et al, 2010[39]
Sanchez-Peña et al, 2012[18]
Garg et al, 2013[40]
Kirkpatrick et al, 2014[16]
Wong et al, 2015[17]
Woo et al, 2015[44]
Diringer et al, 2016[41]
Naraoka et al, 2017[43]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