REVIEW ARTICLES

Richard P. Cambria, MD, Section Editor

A meta-analysis of clinical studies of statins for prevention of abdominal aortic aneurysm expansion

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Background: **Despite the absence of a relationship between cholesterol and abdominal aortic aneurysm (AAA) expansion, there is evidence from a number of studies to suggest that statin therapy may influence AAA expansion, presumably through pleiotropic effects. To confirm whether statin therapy is associated with less AAA expansion, we performed a meta-analysis of clinical controlled studies of statin therapy for prevention of AAA expansion.**

Methods: **To identify all clinical studies of statin therapy vs control (no statins) enrolling patients with small (≤55 mm) AAA, MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched. For each study, data regarding AAA expansion in both the statin and control groups were used to generate standardized mean differences (SMDs; <0 favoring statin therapy; >0 favoring control) and 95% confidence intervals (CIs). Study-specific estimates were combined using inverse variance-weighted averages of logarithmic SMDs in fixed-effects and random-effects models.**

Results: **We identified five clinical controlled studies of statin therapy vs control enrolling patients with small AAA, including no randomized and five observational studies. Our meta-analysis included data on 697 patients with small AAA received statin therapy or no statins. Pooled analysis demonstrated that statin therapy was statistically significantly associated with less expansion rates (random-effects SMD, −0.50; 95% CI, −0.75 to −0.25; $P = .0001$). There was statistically significant trial heterogeneity of results ($P = .03$). Exclusion of any single trial from the analysis did not substantively alter the overall result of our analysis. There was no evidence of significant publication bias ($P = .81$).**

Conclusion: **Statin therapy is associated with less expansion rates in patients with small AAA. To confirm our results and more accurately assess the effect of statins on AAA expansion, a large randomized trial is needed. (J Vasc Surg 2010;52: 1675-81.)**

Although several studies have found an association between the presence of abdominal aortic aneurysm (AAA) and the concentration of total cholesterol,[1,2] there is no clear relationship between total cholesterol and AAA expansion.[3,4] Despite the absence of a relationship between cholesterol and AAA expansion, there is evidence from a number of studies to suggest that statin therapy may be associated with less AAA expansion, presumably through its pleiotropic effects.[5] A meta-analysis by Guessous et al[6] of two cohort studies[7,8] found statin therapy appeared to hold promise for being associated with less AAA expansion. Our preliminary meta-analysis[9] of three observational clinical studies[8,10,11] also suggested that statin therapy was associated with less AAA expansion. Since these meta-analyses[6,9] were conducted, however, a number of clinical studies have provided the association of statin therapy on less AAA expansion. To confirm whether statin therapy is associated with less AAA expansion, we performed an updated meta-analysis of clinical controlled studies of statin therapy for prevention of AAA expansion.

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Competition interest: none.

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METHODS

Search strategy. All clinical studies of statin therapy vs control (no statins) that enrolled patients with small AAA were identified using a two-level search strategy. First, public domain databases, including MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials, were searched using Web-based search engines (PubMed, OVID). Second, relevant studies were identified through a manual search of secondary sources, including references of initially identified articles and a search of reviews and commentaries. All references were downloaded for consolidation, elimination of duplicates, and further analysis.

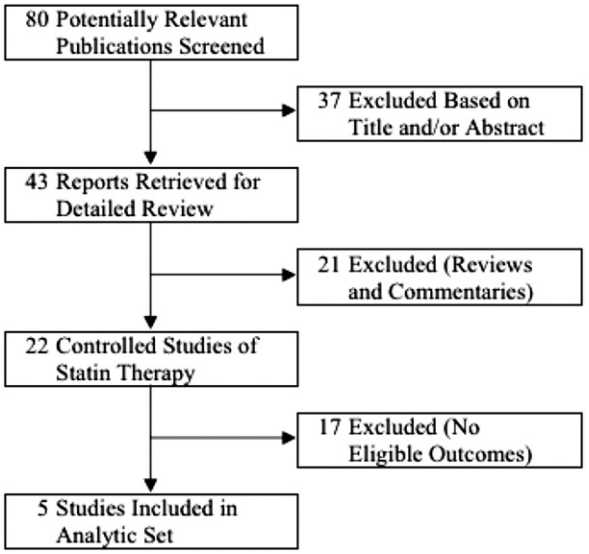

Fig 1. A Quality of Reporting of Meta-analyses (QUROM)[12] flow diagram for the meta-analysis.

The MEDLINE database was searched from January 1966 to December 2009. MeSH keywords included *aortic aneurysm, abdomen,* and *hydroxymethylglutaryl-CoA reductase inhibitors*. Exploding keywords included *abdominal aortic aneurysm, hydroxymethylglutaryl-CoA reductase inhibitors,* and *statin*. The Cochrane Library and Central Register of Controlled Trials (current through December 2009) and the EMBASE database (January 1991 to December 2009) were searched using the OVID exploding keywords *abdominal aortic aneurysm, hydroxymethylglutaryl-CoA reductase inhibitors,* and *statin*.

Study selection and data abstraction. Studies considered for inclusion met the following criteria: the design was a clinical controlled study, the study population comprised patients with small (≤55-mm) AAA, patients received statin therapy vs no statins (control), and main outcomes included AAA expansion. We included not only studies providing expansion rates adjusted for potentially confounding variables but also studies reporting unadjusted expansion rates. A Quality of Reporting of Meta-analyses (QUOROM)[12] flow diagram of the study selection process is illustrated in Fig 1. Data regarding detailed inclusion criteria, statin type, duration of follow-up, and AAA expansion were abstracted (as available) from each individual study. According to the guidance to authors for the preparation of Cochrane Intervention reviews,[13] we imputed missing data (means and standard deviations [SDs]) of expansion rates.

Statistical analysis. For each study, AAA expansion data in the statin and control groups were used to generate standardized mean differences (SMDs; <0 favors statin therapy; >0 favors control) and 95% confidence intervals (CIs). Study-specific estimates were combined using inverse variance-weighted averages of logarithmic SMDs in both fixed-effects and random-effects models. Between-study heterogeneity was analyzed by means of standard χ^2 tests. Where no significant statistical heterogeneity was identified, the fixed-effects estimate was used preferentially as the summary measure. Sensitivity analyses were performed to assess the contribution of each study to the pooled estimate by excluding individual studies one at a time and recalculating the pooled SMD estimates for the remaining studies (leave-one-out meta-analysis). To assess the effect of qualitative heterogeneity in study design on the pooled effect estimate, the effects of statin therapy on AAA expansion were explored separately in studies providing adjusted and unadjusted expansion rates. Publication bias was assessed graphically using a funnel plot and mathematically using an adjusted rank correlation test.[14] All analyses were conducted using Review Manager 5.0,[15] Comprehensive Meta-Analysis 2 (Biostat, Englewood, NJ), and Meta-Analyst 3.0 software.[16]

RESULTS

As outlined in Fig 1, our search identified five clinical controlled studies[7,8,10,11,17] of statin therapy vs control that enrolled patients with small AAA. These included no randomized and five observational studies. Our meta-analysis included data on 697 patients with small AAA received statin therapy or no statins. The baseline characteristics for the patients enrolled in each study are summarized in the Table.

Sukhija et al[7] reported the size of AAAs at long-term follow-up in 130 patients with AAAs who were not treated surgically and in those treated with and without statins. At long-term follow-up of patients treated with statins, serum low-density lipoprotein cholesterol decreased from 142 ± 18 to 90 ± 17 mg/dL ($P < .001$), serum high-density lipoprotein cholesterol increased from 43 ± 6 to 46 ± 6 mg/dL ($P < .001$), and serum triglycerides decreased from 137 ± 19 to 120 ± 20 mg/dL ($P < .001$). AAA sizes were measured by computed tomography (CT) scans at baseline and at the last follow-up and were 46 ± 6 mm at baseline and 45 ± 6 mm at the 23 ± 7-month follow-up in patients treated with statins (P = NS) and 45 ± 6 mm at baseline and 53 ± 6 mm at the 24 ± 7-month follow-up in patients not treated with statins ($P < .001$). Mortality at long-term follow-up was 5% (45 ± 8 months) in patients with AAAs treated with statins and 16% (44 ± 8 months) in those without statin treatment ($P < .05$).

A retrospective analysis by Schouten et al[8] included 150 patients under surveillance with a follow-up (every 6 to 12 months by means of ultrasound imaging) for aneurysm expansion of at least 12 months and a minimum of three diameter evaluations. Multiple regression analysis (age, gender, AAA diameter at initial presentation, nonsteroidal anti-inflammatory drug use, statin use, and cardiovascular risk factors were used as independent variables), weighted with the number of observations (ie, number of ultrasound measurements), was performed to test the influence of statins on AAA expansion rate. Statin users had a mean

Table. Baseline patient characteristics

Variables	*Karlsson 2009*[17]	*Mosorin 2008*[11]	*Schlösser 2008*[10]	*Schouten 2006*[8]	*Sukhija 2006*[7]
Primary outcomes	Correlation between plasma levels of IL-6, MMP-9, and CRP and with AAA expansion	Association of statins with AAA expansion and aneurysm repair or rupture	Rupture rates, risks of mortality, and predictors of AAA expansion	Association of statins with AAA expansion	Association of statins with mortality and AAA expansion
Statin type	NR	NR	NR	Atorvastatin Fluvastatin Pravastatin Simvastatin	Atorvastatin Simvastatin
Patients, No.					
Statins	85	34	63[a]	59	75
No statins	127	87	84	91	55
AAA diameter, mm					
Statins	NR	39 ± 7	NR	40 ± 9	46 ± 6
No statins	NR	39 ± 6	NR	37 ± 7	45 ± 6
Total	40 (37-44)[b]	. . .	39 ± 7	. . .	. . .
P	NR	.94	NR	.02	NS
AAA surveillance	US	US	US	US	CT
Follow-up					
Statins	NR	NR	NR	2.9 y[c]	23 ± 7 mo
No statins	NR	NR	NR	3.2 y[c]	24 ± 7 mo
Total	≥18 mon	3.6 ± 2.2 y	4.0 ± 2.5 y	. . .	. . .
P	NR	NR	NR	.49	NS
Age, y					
Statins	NR	71 ± 8	NR	69 ± 8	67 ± 8
No statins	NR	70 ± 8	NR	69 ± 8	66 ± 8
Total	71 (67-75)[d]	. . .	65 ± 8	. . .	. . .
P	NR	.73	NR	.94	NS
Female, %					
Statins	NR	12	NR	14	16
No statins	NR	10	NR	18	18
Total	23	. . .	11	. . .	. . .
P	NR	.76	NR	.44	NS
CAD, %					
Statins	NR	76	NR	51	69
No statins	NR	51	NR	48	64
Total	31	. . .	39	. . .	. . .
P	NR	.01	NR	NR	NS
CVD, %					
Statins	NR	21	NR	14	NR
No statins	NR	13	NR	12	NR
Total	14	. . .	14	. . .	. . .
P	NR	.27	NR	1.00	NR
DM, %					
Statins	NR	15	NR	15	24
No statins	NR	10	NR	11	22
Total	4	. . .	24	. . .	. . .
P	NR	.53	NR	.32	NS
Hypertension, %					
Statins	NR	44	NR	47	64
No statins	NR	44	NR	40	62
Total	59	. . .	87	. . .	. . .
P	NR	1.00	NR	.30	NS
COPD, %					
Statins	NR	21	NR	29	NR
No statins	NR	37	NR	26	NR
Total	6	. . .	. . .	. . .	. . .
P	NR	.13	NR	.85	NR
PAD, %					
Statins	NR	9	NR	29	NR
No statins	NR	8	NR	10	NR
Total	. . .	. . .	16	. . .	. . .
P	NR	1.00	NR	.01	NR

Table. Continued

Variables	*Karlsson 2009*[17]	*Mosorin 2008*[11]	*Schlösser 2008*[10]	*Schouten 2006*[8]	*Sukhija 2006*[7]
Smoking, %					
Statins	NR	62	NR	68	28
No statins	NR	87	NR	73	25
Total	38	. . .	40	40	. . .
P	NR	NR	NR	.72	NS
Medication					
β-blocker, %	. . .	. . .	. . .	. . .	. . .
Statins	NR	71	NR	41	77
No statins	NR	49	NR	32	67
Total					
P	NR	.43	NR	.28	NS
ACE inhibitor, %					
Statins	NR	15	NR	20	75
No statins	NR	10	NR	29	71
Total	30	. . .	. . .	. . .	. . .
P	NR	.53	NR	.24	NS

AAA, Abdominal aortic aneurysm; *ACE,* angiotensin converting enzyme; *CAD,* coronary artery disease; *COPD,* chronic obstructive pulmonary disease; *CRP,* C-reactive protein; *CT,* computed tomography; *CVD,* cerebrovascular disease; *DM,* diabetes mellitus; *IL-6,* interleukin-6; *MMP-9,* matrix metalloproteinase-9; *NR,* not reported; *NS,* not significant; *PAD,* peripheral artery disease; *US,* ultrasound imaging.

[a]2% of the patients used nonstatin drugs.

[b]Median and range.

[c]Median.

[d]Median and interquartile range.

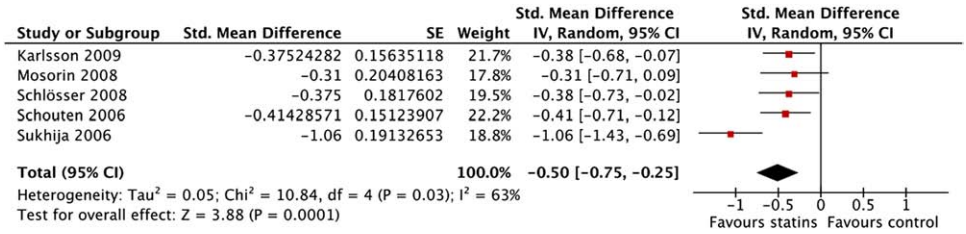

Fig 2. Forrest plot shows the standardized mean difference of abdominal aortic aneurysm expansion rates. *CI,* Confidence interval; *IV,* inverse variance; *SE,* standard error.

1.16-mm/y (95% CI, 0.33-1.99 mm/y) lower AAA expansion rate compared with nonusers.

In an observational cohort study by Schlösser et al,[10] AAA ultrasound measurements (every 12 months for AAAs with a diameter between 30 and 39 mm and every 6 months for AAAs with a diameter of 40 to 55 mm) were performed for a period of >6 months in 147 of 230 patients with a 30- to 55-mm AAA. Multivariable regression analysis was performed to calculate the effects of demographic patient characteristics, initial AAA diameter, and cardiovascular risk factors on AAA growth. Patients using lipid-lowering drugs (2% of the patients used nonstatins) had a mean 1.2-mm/y (95% CI, 2.34-0.060 mm/y) lower AAA expansion rate than nonusers of these drugs. After adjustments for age, no significant association between lipid-lowering drug use and survival time was found ($P = .30$).

The retrospective study by Mosorin et al[11] included 121 patients with a ≥30-mm AAA undergoing ultrasound surveillance (at 3- to 12-month intervals according to AAA diameter and patients' conditions) for at least 1 year. The mean aneurysm expansion rate did not differ between patients treated and not treated with statins (1.9 ± 1.8 mm/y vs 2.6 ± 2.4 mm/y, $P = .27$). In a study by Karlsson et al,[17] 213 patients with a 35 to 49-mm AAA were followed-up with ultrasound examination every 6 months for a minimum of 18 months. Patients receiving statin medication had a lower median expansion rate than patients not taking statins of 1.6 vs 2.5 mm/y (95% CI for the difference, 0.03-1.5 mm/y; $P = .008$).

Although Sukhija et al[7] and Mosorin et al[11] provided both means and SDs of expansion rates, Schouten et al[8] and Schlösser et al[10] reported means and 95% CIs instead of SDs, and Karlsson et al[17] provided a median instead of a mean and a 95% CI instead of a SD. According to the guidance to authors for the preparation of Cochrane Intervention reviews,[13] we imputed a missing mean in the study by Karlsson et al[17] and missing SDs in the studies by Schouten et al,[8] Schlösser et al,[10] and Karlsson et al.[17]

Pooled analysis demonstrated statistically significantly lower expansion rates with statin therapy (random-effects

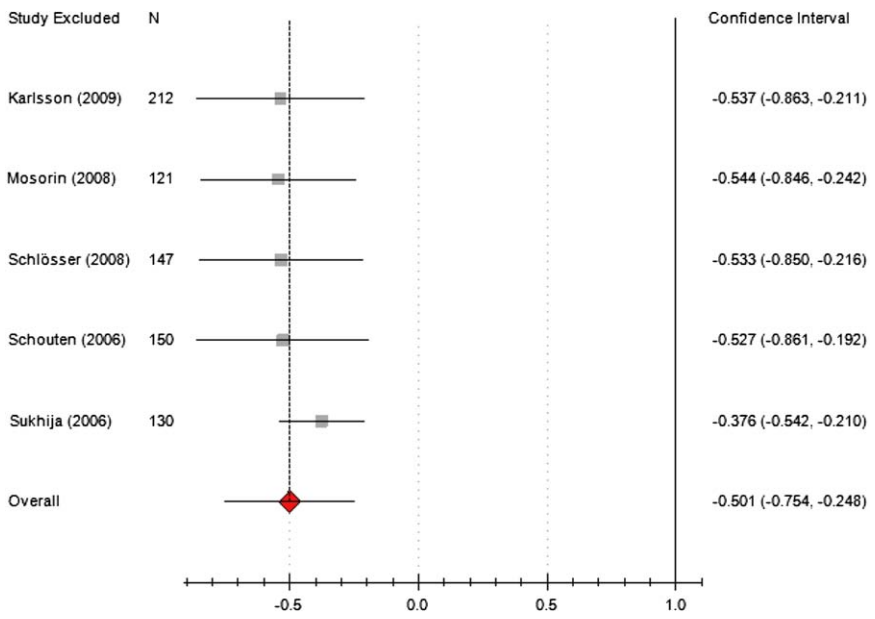

Fig 3. Leave-one-out meta-analysis.

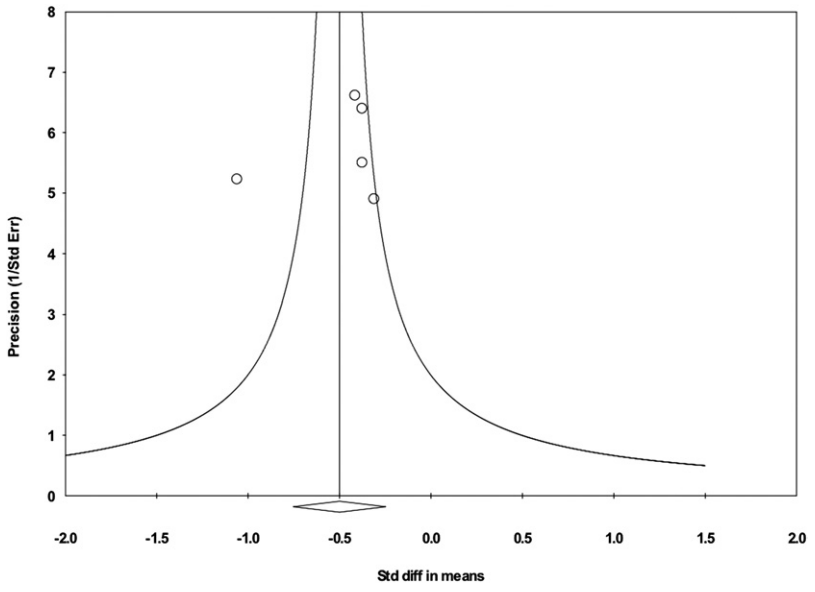

Fig 4. Funnel plot shows the precision by the standardized mean difference.

SMD, −0.50; 95% CI, −0.75 to −0.25; $P = .0001$; Fig 2). There was statistically significant trial heterogeneity of results ($P = .03$). When data from studies providing adjusted and unadjusted expansion rates were separately pooled, statin therapy was associated with lower expansion rates that remained statistically significant for adjusted studies (fixed-effects SMD, −0.40; 95% CI, −0.63 to −0.17; $P = .0006$; P for heterogeneity = .87) and for unadjusted studies (random-effects SMD, −0.58; 95% CI, −1.04 to −0.12; $P = .01$; P for heterogeneity = .008). Exclusion of any single trial from the analysis (leave-one-out meta-analysis) did not substantively alter the overall result of our analysis (Fig 3).

To assess publication bias, we generated a funnel plot of the effect size vs the reciprocal of the standard error for each study (Fig 4). Although the adjusted rank correlation test[14] did not indicate publication bias ($P = .81$), there is clearly limited power to detect such bias and accordingly it is difficult to assess, given the small number of only five studies examined.

DISCUSSION

Our analysis showed that statin therapy was associated with lower expansion rates in patients with small AAA, which suggests that statins may reduce AAA expansion. Despite the absence of a clear relationship between serum cholesterol level and AAA expansion, statin therapy is expected to prevent AAA development because the pleiotropic effects of statins include an anti-inflammatory effect, antioxidative effect, and the reduction of matrix metalloproteinase (MMP) secretion.[18] Statins reduce the tissue levels of MMP-9 in human AAA specimens explanted for culture.

Nagashima et al[19] suggested that cerivastatin could directly modulate the biology of the AAA wall and suppressed MMP-9 production in the AAA wall by inhibiting the activation of neutrophils and macrophages. Evans et al[20] demonstrated a reduction in MMP-9 levels in the AAA wall in patients randomized to simvastatin. Furthermore, Wilson et al[21] showed that simvastatin, pravastatin, and atorvastatin decreased concentrations of MMP-3 and MMP-9 in the anterior AAA wall of humans undergoing asymptomatic repair. In experimental studies, simvastatin suppressed AAA progression in a mouse model, accompanied by a reduction of MMP-9 and an increase of tissue inhibitors of metalloproteinase-1, whereas inflammatory cell infiltration was not inhibited.[22,23]

Shiraya et al[24] demonstrated an inhibitory effect of atorvastatin in an elastase-induced rat AAA model. However, atorvastatin suppressed macrophage recruitment into the vascular wall through the inhibition of intercellular adhesion molecule-1 and monocyte chemoattractant protein-1 expression, leading to the inhibition of MMP-12, but not MMP-9 expression. Therefore, it is suggested that the suppression of AAA development by atorvastatin was mainly dependent on its anti-inflammatory effect.[18]

Karlsson et al[25] demonstrated that patients taking acetylsalicylic acid (ASA) had lower expansion rates than those not taking ASA (0.18 vs 0.26 cm/y, $P = .004$) and that patients taking statins and ASA together had a significantly reduced expansion rate than patients who did not take statins or ASA (0.14 vs 0.27 cm/y, $P < .001$). Statins and ASA have different anti-inflammatory properties, which might explain the complementary effect, although ASA seems to be more effective than statins (0.19 vs 0.23 cm/y).

Meanwhile, an association of oxidative stress with the formation of AAA has been suggested. Reactive oxygen and nitrogen species are increased in the human aneurysmal wall compared with the normal aorta and adjacent nonaneurysmal aortic wall.[26] Overexpressed reactive oxygen species and nitric oxide increased the expression of MMPs through the activation of nuclear factor κB and induced apoptosis of vascular smooth muscle cells in the aneurysm wall.[27-29] Statins may improve endothelial function through their antioxidant effects.

The results of the present meta-analysis are consistent with and strengthen those of previous meta-analyses.[6,9] Pooled results of two cohort studies[7,8] in the meta-analysis by Guessous et al,[6] representing 280 patients, showed a significant decrease of expansion rate, with a fixed-effects mean difference (MD) of −2.97 mm/y (95% CI, −5.83 to −0.11 mm/y). Pooled analysis of three observational clinical studies[8,10,11] in our preliminary meta-analysis,[9] representing 418 patients, also demonstrated a significant reduction in expansion rate with statin therapy relative to control, with a random-effects MD of −1.00 mm/y (95% CI, −1.54 to −0.47 mm/y; $P = .0002$).

In the present meta-analysis, we combined five studies, representing 697 patients, and the pooled result was robust in sensitivity analyses. Although the SMDs of AAA expansion rates were similar (−0.41 to −0.31) in four[8,10,11,17] of the five studies included in the present meta-analysis, only the study by Sukhija et al[7] provided −1.06 of the SMD. The mean or median diameters of the baseline AAA were ≤40 mm in the four studies,[8,10,11,17] but in the study by Sukhija et al,[7] the mean diameter was 46 mm in the statin group and 45 mm in the control group. These findings suggest that the inhibitory effect of statin therapy for AAA expansion may depend on the diameter of AAA.

Our analysis, however, must be viewed in the context of its limitations. The major limitation of our study is that we combined only observational studies, and therefore, the treatment strategy was not based on randomized assignment. Our findings are subject to selection bias and confounding. To minimize these biases, Schouten et al[8] and Schlösser et al[10] used a multivariate linear regression model and provided not unadjusted but adjusted effect estimates. Nevertheless, hidden bias may remain because of the influence of unmeasured confounders. The other three studies[7,11,17] provided only unadjusted effect estimates. In nonrandomized observational studies, it is always necessary to adjust for confounding, otherwise the results are subject to some degree of bias. To confirm our results and more accurately assess the effect of statins on AAA expansion, a large randomized trial is needed. Because most patients with AAA may have indications for statin therapy, they are evaluated for these indications and statin therapy should be started if such indications are present. In the absence of any indications for statin therapy, the use of statins could be considered based on what appears to be a modest inhibitory effect on aneurysm expansion.

AUTHOR CONTRIBUTIONS

Conception and design: HT, TU
Analysis and interpretation: HT, MM
Data collection: MM
Writing the article: HT
Critical revision of the article: TU
Final approval of the article: HT, MM, TU
Statistical analysis: HT, MM
Obtained funding: Not applicable
Overall responsibility: HT

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