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Effects of Statin Therapy on Abdominal Aortic Aneurysm Growth: A Meta-analysis and Meta-regression of Observational Comparative Studies CME

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WHAT THIS PAPER ADDS

- The claim of a reduction in abdominal aortic aneurysm (AAA) growth rate with statin therapy is based on low-quality evidence and was not found to be significant on meta-analysis of a few high-quality observational studies. Based on the present updated meta-analysis, statin therapy is likely effective in the prevention of growth of small AAAs. Statin therapy may be more beneficial in reducing growth rate as the baseline diameter increases.

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ABSTRACT

Objective: To determine whether statin therapy reduces the growth rate of small abdominal aortic aneurysms (AAAs).
Design: A meta-analysis and a meta-regression of comparative studies.
Materials: Eligible studies were randomized controlled trials or observational comparative studies of statin therapy versus placebo or no statin, enrolling individuals with small (<55 mm in diameter) AAAs and reporting AAA growth rate as an outcome.
Methods: Study-specific estimates (standardized mean differences [SMDs]) were combined in the fixed- and random-effects model.
Results: Seven adjusted and 4 unadjusted observational comparative studies enrolling 4647 patients with a small AAA were identified. Pooled analysis of all 11 studies suggested a significant reduction in AAA growth rate among patients assigned to statin therapy versus no statin (SMD, −0.420; 95% confidence interval [CI], −0.651 to −0.189). Combining the 7 high-quality studies providing adjusted data for growth rates generated an attenuated but still statistically significant result favoring statin therapy (SMD, −0.367; 95% CI, −0.566 to −0.168). The meta-regression coefficient for the baseline diameter was statistically significant (−0.096; 95% CI, −0.132 to −0.061).
Conclusion: Statin therapy is likely effective in prevention of the growth of small AAAs, and may be more beneficial as the baseline diameter increases.

Although several studies have found an association between the presence of an abdominal aortic aneurysm (AAA) and total cholesterol,[1,2] there is no clear relationship between total cholesterol and AAA growth rate.[3–5] Despite this, there is evidence from a number of studies to suggest that statins may influence aneurysm growth rates, presumably via these pleiotropic effects.[6] Previous meta-analyses[6–11] of a small number (≤7) of observational comparative studies also suggest a reduction in AAA growth rate in patients taking a statin. This claim, however, is based on low-quality evidence and was not significant on meta-analysis of only 4 high-quality studies.[10] On the other hand, based on our most recent preliminary meta-analysis[11] of another set of 4 high-quality studies, we found that statin therapy is associated with lower growth rate in patients with a small AAA. Herein, we report the

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results of an updated formal meta-analysis of comparative studies of statin therapy for reduction of AAA growth rate. To assess the impact of initial diameter of AAA or percentage of female patients on AAA growth rates, we also performed a meta-regression analysis.

Material and Methods

Search strategy

All randomized controlled trials and observational comparative studies of statin therapy enrolling patients with small AAAs were identified using a 2-level search strategy. First, public domain databases, including MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials, were searched through February 2012 using Web-based search engines (PubMed, OVID). Keywords included *abdominal aortic aneurysm*; and *statin*, *hydroxymethylglutaryl-CoA reductase inhibitor*, *atorvastatin*, *cerivastatin*, *fluvastatin*, *lovastatin*, *mevastatin*, *pitavastatin*, *pravastatin*, *rosuvastatin*, or *simvastatin*. 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.

Study selection and data abstraction

Studies considered for inclusion met the following criteria: the design was a randomized controlled trial or observational comparative study; the study population was patients with a small (<55 mm in diameter) AAA; patients were assigned to statin therapy versus placebo or no statin; and outcomes included AAA growth rate. Data regarding detailed inclusion criteria, duration of follow-up, and AAA growth rates were abstracted (as available) from each individual study. When adjusted growth rates or adjusted mean differences (MDs) of growth rates were available, they were extracted preferentially instead of crude (unadjusted) data for growth rates. Where standard deviations (SDs) were unavailable, missing SDs were imputed according to the Cochrane Handbook.[12]

Statistical analysis

For each study, data regarding AAA growth rates were used to generate standardized MDs (SMDs) and 95% confidence intervals (CIs). Study-specific estimates combined using inverse variance-weighted averages of logarithmic SMDs in the fixed- and random-effects model. Between-study heterogeneity was analyzed by means of standard χ^2 tests. Where nonsignificant statistical heterogeneity was identified, the fixed-effect 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. To assess the impact of baseline AAA diameter or female percentage among the studies on the study-specific estimate, we performed a restricted maximum likelihood meta-regression analysis. Meta-regression graphs depict the effect of statin therapy on the outcome (plotted as a SMD of growth rates on the *y*-axis) as a function of a given factor (plotted as a mean of the baseline diameter or a female percentage on the *x*-axis). Meta-regression coefficients (slopes of meta-regression lines) show the estimated increase in SMD per unit increase in the covariate. A negative coefficient would indicate that as a given factor increases the SMD decreases, i.e. statin therapy is more beneficial in reducing the outcome of interest. Publication bias was assessed graphically using a funnel plot and mathematically using an adjusted rank-correlation test. All analyses were conducted using the metareg in Stata SE release 11.2 (StataCorp LP, College Station, TX) and Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ).

Results

Search results

Initial electronic search identified 113 potentially relevant publications, all of which were reviewed in detail. As a consequence, we selected 4 unadjusted and 7 adjusted observational comparative studies of statin therapy enrolling patients with a small AAA.[13–23] No randomized controlled trial was identified. In total, our meta-analysis included data on 4647 patients assigned to statin therapy or no statin. The trial design, female percentage, follow-up duration, baseline diameter, growth rate, and their MDs are summarized in Table 1.

Primary meta-analysis

Pooled analysis of all the 11 studies demonstrated a statistically significant reduction in AAA growth rates with statin therapy relative to no statin in the random-effects model (SMD, −0.420; 95% CI, −0.651 to −0.189; $P < 0.001$; P for heterogeneity <0.001; Fig. 1). To assess publication bias, we generated a funnel plot of the effect size versus the precision (reciprocal of the standard error) for each study (Fig. 2). There was no evidence of significant publication bias ($P = 0.276$).

Sensitivity analysis

To assess the impact of qualitative heterogeneity in study design and patient selection on the pooled effect estimate, we performed several sensitivity analyses. First, we excluded 4 low-quality studies[13–15,21] reporting unadjusted growth rates. Combining the remaining 7 high-quality studies providing adjusted data for growth rates generated an attenuated but still statistically significant result favoring statin therapy (random-effects SMD, −0.367; 95% CI, −0.566 to −0.168; $P < 0.001$; P for heterogeneity = 0.005; Fig. 3). In general, exclusion of any single study from the analysis did not substantively alter the overall result of our analysis (Fig. 4).

Meta-regression analysis

Meta-regression analysis was performed to determine whether the effects of statin therapy were modulated by the pre-specified factors. The meta-regression coefficient for the female percentage (slope of the meta-regression line) was not statistically significant (−0.016; 95% CI, −0.462 to 0.135, $P = 0.247$; Fig. 5). The poor fit appears to be the result from a dramatic outlier (study by Sukhija et al.[21]) in addition to a substantial scatter about the line for the other studies. If the result of the study by Sukhija et al.[21] is eliminated, the meta-regression coefficient is statistically significant (−0.019; 95% CI, −0.034 to −0.003, $P = 0.022$). On the other hand, the coefficient for the baseline diameter was statistically significant (−0.096; 95% CI, −0.132 to −0.061; $P < 0.001$: Fig. 6), which indicates that statin therapy is more beneficial in reducing growth rate as the baseline diameter increases. The *x*-axis intersection of the 95% CI upper limit was 35.9 mm, which suggests that statin therapy is significantly beneficial in reducing growth rate when the baseline diameter is ≥36.0 mm.

Table 1
Trial design, female percentage, follow-up duration, baseline diameter, growth rate, and their mean differences.

Study	Design	Adjustment statistics	Patient number		Female (%)	Follow-up duration		Baseline diamter (mm)		Growth rate			Mean difference
			Statin	No statin		Statin	No statin	Statin	No statin	Unit	Statin (mean ± SD)	No statin (mean ± SD)	
Badger 2011	Retrospective	Unadjusted	92	51	15.1	Follow-up scans (≥3 months apart): median, 5 (range, 2–17)		39 ± 7		%/y	4.5 ± 6.0[a]	7.5 ± 6.0[a]	−3.00 (95% CI, −5.05 to −0.95)[a,b]
Ferguson 2010	Prospective observational	Unadjusted	349	303	6.4	Median, 5 (IQR, 3–6) years		Median, 33.9 (IQR, 31.3–37.6)	Median, 33.0 (IQR, 31.0–36.5)	NA	1.63 ± 2.846[a,c]	1.34 ± 1.447[a,c]	0.29 (95% CI, −0.06 to 0.64)[a,b]
Karlsson 2009	Retrospective	Unadjusted	85	127	23.5	≥18 months		Median, 40 (range, 37–44)		mm/y	1.6 ± 2.40[a]	2.5 ± 2.40[a]	−0.77 (95% CI, −1.5 to −0.03)[a]
Karrowni 2011	Retrospective	Multivariate linear regression	136	75	33.2	Median, 1.04 (IQR, 1.01–1.10) years	Median, 1.04 (IQR, 1.02–1.12) years	Median, 41 (IQR, 37–44)	Median, 41 (IQR, 37–43)	%/y	−0.7 ± 12.8	7.5 ± 9.3	−8.20 (95% CI, −11.49 to −4.91)[b]
Mosorin 2008	Retrospective	Multivariate linear regression	34	87	10.7	3.6 ± 2.2 years		38.7 ± 7.0	39.3 ± 6.3	mm/y	1.9 ± 1.8	2.6 ± 2.4	−0.70 (95% CI, −1.59 to 0.19)[b]
Periard 2012	Retrospective	Multivariate linear regression	50	44	10.6	43 ± 29 months	33 ± 24 months	39.3 ± 7.6	40.7 ± 7.7	mm/y	2.91 ± 2.09[a]	4.37 ± 3.45[a]	−1.06 (95% CI, −2.17 to 0.04)
Schouten 2006	Retrospective	Multivariate linear regression	59	91	16.0	Median, 2.9 years	Median, 3.2 years	40 ± 8.5	37 ± 7.0	mm/y	2.0 ± 2.9[a]	3.6 ± 2.9[a]	−1.16 (95% CI, −1.99 to −0.33)
SMART 2008	Prospective observational	Multivariate linear regression	63	84	10.9	Median, 3.3 (range, 0.5–11.1) years		39 ± 6.8		mm/y	NA		−1.20 (95% CI, −2.34 to −0.060)
Sukhija 2006	Unclear	Unadjusted	75	55	16.9	23 ± 7 months	24 ± 7 months	46 ± 6	45 ± 6	mm	−1 ± 6[a,b]	8 ± 6[a,b]	−9.0 (95% CI, −11.09 to −6.91)[a,b]
Sweeting 2010	Prospective observational	Mixed-effects linear growth model adjusted for potential confounders	21	1535	32.6	Mean, 1.9 years		43 ± 7		mm/y	1.92 ± 2.50	2.81 ± 2.50	−0.90 (95% CI, −1.98 to 0.18)[b]
Thompson 2010	Prospective observational	Flexible hierarchical model	383	848	5.9	Median, 3.09 (IQR, 1.97–6.05) years		Median, 35 (IQR, 31–42)		mm/y	NA		−0.29 (95% CI, −0.66 to 0.08)
Total			1347	3300									

CI, confidence interval; IQR, interquartile range; NA, not available; SD, standard deviation.
[a] Unadjusted data.
[b] Data calculated by us.
[c] Data provided directly by the authors (personal communication).

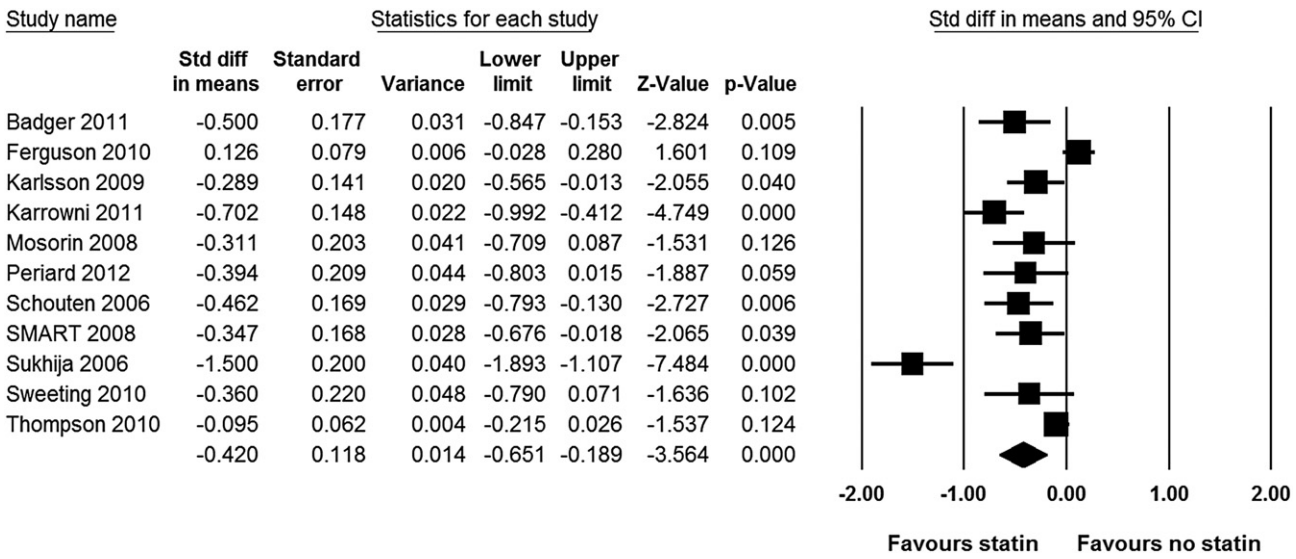

Figure 1. Forest plot of growth rates of abdominal aortic aneurysm among patients assigned to statin therapy versus no statins from all the 11 studies (primary meta-analysis).

Discussion

The results of our analysis suggest that statin therapy may restrain growth of small AAAs. This result was robust in sensitivity analyses, even eliminating unadjusted studies. The reduction in AAA growth rate by statin therapy may prevent aneurysm rupture or the need for repair. Despite the absence of a clear relationship between serum cholesterol level and AAA growth rate, statin therapy is expected to prevent AAA development, because the pleiotropic effects of statins include an anti-inflammatory effect, anti-oxidative effect, and reduction of matrix metalloproteinase (MMP) secretion.[24] Karlsson et al.[25] demonstrated that patients taking acetylsalicylic acid (ASA) had lower growth rates than those not taking ASA (0.18 versus 0.26 cm/y; $P = 0.004$), and that patients taking statins and ASA together had a significantly reduced growth rate compared to patients who did not take statins or ASA (0.14 versus 0.27 cm/y, $P < 0.001$). Statins and ASA have different anti-inflammatory properties, which may explain the complementary effect, although ASA seems to be more effective than statins (0.19 versus 0.23 cm/y). In the most recent meta-analysis of 7 studies by Twine and Williams,[10] although there was a significant reduction in the AAA growth rate in patients taking statins in the overall analysis (SMD, −0.37 mm/year; 95% CI, −0.65 to −0.08 mm/year; $P = 0.01$), the 4 high-quality studies (achieving at least 7 stars from a maximum of 9 assessed using the Newcastle–Ottawa Scale[26]) in this analysis showed no significant difference in AAA growth between the 2 groups (SMD, −0.14 mm/year; 95% CI, −0.33 to 0.05 mm/year; $P = 0.16$). The present meta-analysis, however, is more comprehensive and includes 7 adjusted studies (reporting adjusted growth rates or adjusted MDs of growth rates).

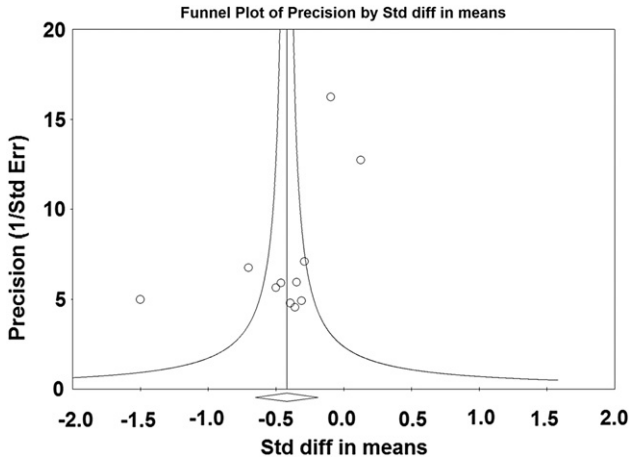

Figure 2. Funnel plot of precision (reciprocal of standard error) by standardized mean difference of growth rates of abdominal aortic aneurysm between patients assigned to statin therapy versus no statins. There was no evidence of significant publication bias ($P = 0.276$).

Among the 11 studies included in the present meta-analysis, the greatest baseline AAA diameter (mean, 46 mm) and the most favorable effect of statin therapy on growth rate (SMD, −1.500) were abstracted from the study by Sukhija et al.,[21] whereas the smallest diameter (mean, 33.5 mm) and the only unfavorable effect (SMD, 0.126) were extracted from the study by Ferguson et al.[14] These findings suggest that the inhibitory effect of statin therapy on AAA growth may depend on the baseline AAA diameter. Indeed, our meta-regression analysis demonstrates that statin therapy is more beneficial in reducing growth rate as the baseline diameter increases, and that statin therapy is significantly beneficial in reducing the growth rate when the baseline diameter is ≥36.0 mm (Fig. 6). Our results suggest that anti-inflammatory effects of statins may contribute toward restraining AAA growth. Larger size of AAA is likely to be associated with higher inflammatory status, because of significant positive correlations between circulating biomarkers of inflammation (C-reactive protein [CRP][27] and interleukin-6 concentrations[28,29]) and AAA size. The absolute vascular risk reduction associated with statin therapy (rosuvastatin within the JUPITER trial[30]) is greater among those with higher baseline high-sensitivity CRP levels. Effects of statins in reducing growth rate may also be more beneficial in AAAs with a greater baseline diameter because of the higher inflammatory status. Our meta-regression analysis also showed a trend toward more beneficial effects of statin therapy in reducing the growth rate as the proportion of female patients increases (Fig. 5). The most recent meta-analysis[31] of 18 randomized clinical trials, however, indicated that statins decrease cardiovascular events and all-cause mortality similarly in women and men. Further analysis is needed in terms of effects of statin therapy on small AAAs in female patients.

Our analysis must be viewed in the context of its limitations. We used data from no randomized controlled trials and 11

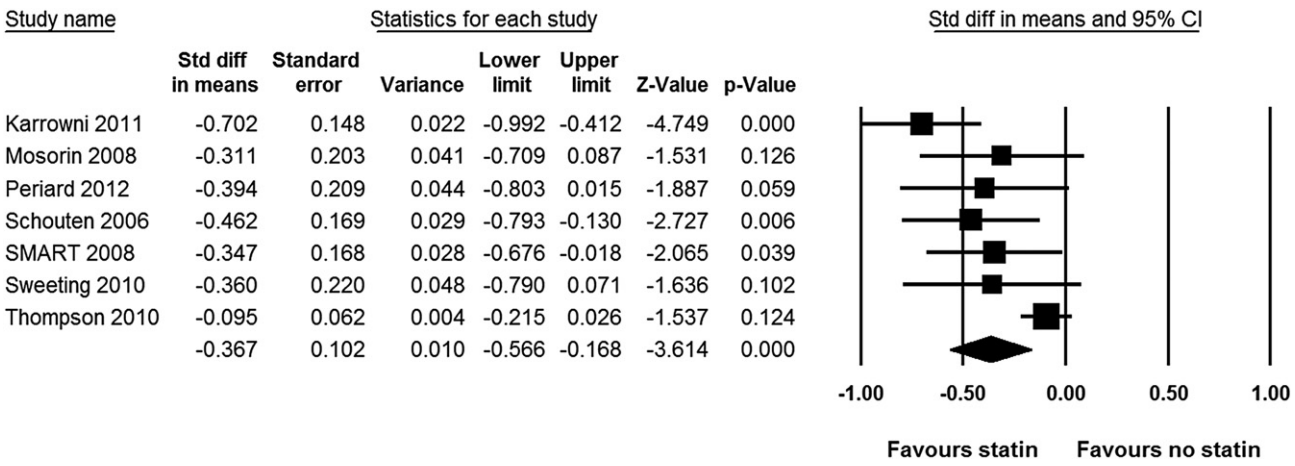

Figure 3. Forest plot of growth rates of abdominal aortic aneurysm among patients assigned to statin therapy versus no statins from the 7 high-quality studies providing adjusted data.

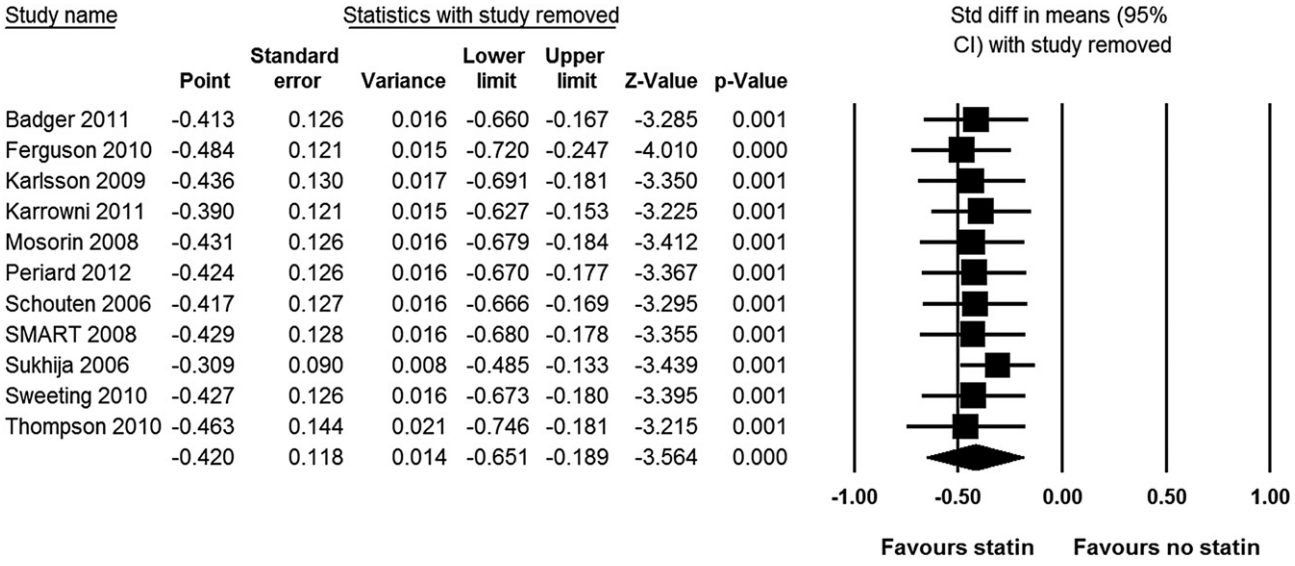

Figure 4. One-study-removed meta-analysis of growth rates of abdominal aortic aneurysm among patients assigned to statin therapy versus no statins.

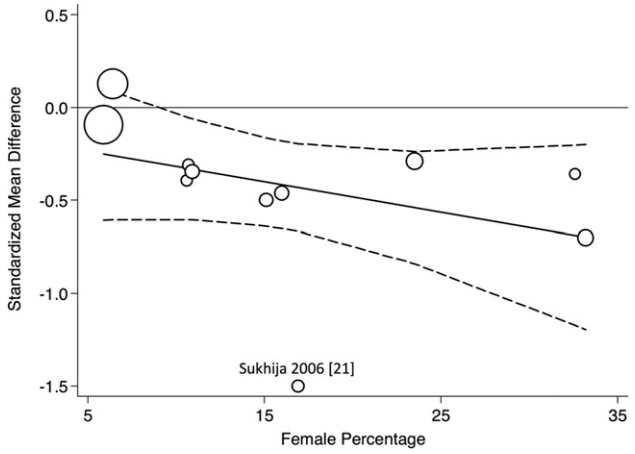

Figure 5. Meta-regression plot for standardized mean difference of growth rates of abdominal aortic aneurysm by proportion of females (%). The meta-regression coefficient for the female percentage (slope of the meta-regression line) was not statistically significant (−0.016; 95% confidence interval [CI], −0.462 to 0.135, $P = 0.247$). If the result of the study by Sukhija et al.[21] is eliminated, the meta-regression coefficient is statistically significant (−0.019; 95% CI, −0.034 to −0.003, $P = 0.022$).

observational comparative studies. Patients enrolled in randomized trials may not be representative of those typically seen in clinical practice. However, because randomized trials balance both known and unknown confounders across treatment groups, this is the study design least vulnerable to bias. As potential biases are likely to be greater for observational studies compared to randomized trials, results should always be interpreted with caution when they are included in reviews and meta-analyses.[32] Particular concerns arise with respect to differences between patients in different intervention groups (selection bias) and studies that do not explicitly report having had a protocol (reporting bias). Unlike for randomized trials, it will usually be appropriate to analyze adjusted, rather than unadjusted, effect estimates, i.e. analyses that attempt to 'control for confounding'. To reduce the effect of treatment-selection bias and potential confounding in observational studies, rigorous adjustment for significant differences in the baseline characteristics of patients could be conducted. Further, not unadjusted but adjusted estimates would be pooled in a meta-analysis including observational studies. Although we combined 4 unadjusted and 7 adjusted data sets from observational comparative studies in the primary meta-analysis, the sensitivity analysis of only the 7 adjusted data sets also demonstrated a statistically significant benefit of statin therapy on AAA growth rate.

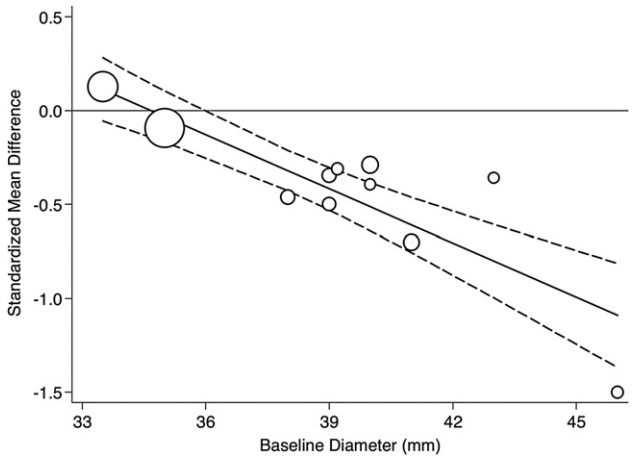

Figure 6. Meta-regression plot for standardized mean difference of growth rates of abdominal aortic aneurysm by baseline diameter (mm). The coefficient for the baseline diameter (slope of the meta-regression line) was statistically significant (−0.096; 95% confidence interval [CI], −0.132 to −0.061; $P < 0.001$), and the *x*-axis intersection of the 95% CI upper limit was 35.9 mm.

Nevertheless, hidden bias may remain because of the influence of unmeasured confounders even after appropriate adjustment. Further, our results may be influenced by a publication bias favoring statin therapy. This risk was minimized through an exhaustive search of the available literature in our analysis. Though the statistical tests did not indicate publication bias, there is clearly limited power to detect such bias, given the small number of studies examined.

Conclusions

We found that, based on a meta-analysis, statin therapy is likely effective in the prevention of growth of small (<55 mm in diameter) AAAs. To confirm our results and more accurately assess the effect of statins on AAA growth, however, a large randomized trial is needed. As most patients with AAA have indications for statin therapy, all patients should be evaluated and statin therapy should be started if such indications are present. In the absence of indications, the use of statins could still be considered based on what appears to be an inhibitory effect on AAA growth.

Disclosures

None.

Funding

None.

Conflict of Interest

None.

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