All authors have no conflict of interests. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

References

[1] Hsieh Shiau-Fu, Hu Gwo-Chi, Chuang Yao-Chia, Chen Chun-Yen, Hu Yu-Ning. The effects and safety of exercise training in subjects with chronic heart failure—do elder subjects gain similar benefits? Int J Gerontol 2010;4:165–70.
[2] Davies EJ, Moxham T, Rees K, et al. Exercise training for systolic heart failure: Cochrane systematic review and meta-analysis. Eur J Heart Fail 2010;12:706–15.
[3] van Tol BA, Huijsmans RJ, Kroon DW, Schothorst M, Kwakkel G. Effects of exercise training on cardiac performance, exercise capacity and quality of life in patients with heart failure: a meta-analysis. Eur J Heart Fail 2006;8:841–50.
[4] O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439–50.
[5] Forman DE, Clare R, Kitzman DW, et al. Relationship of age and exercise performance in patients with heart failure: the HF-ACTION study. Am Heart J 2009;158:S6–S15.
[6] Owen A, Croucher L. Effect of an exercise programme for elderly patients with heart failure. Eur J Heart Fail 2000;2:65–70.
[7] Witham MD, Gray JM, Argo IS, Johnston DW, Struthers AD, McMurdo ME. Effect of a seated exercise program to improve physical function and health status in frail patients (greater-than or equal to) 70 years of age with heart failure. Am J Cardiol 2005;95:1120–4.
[8] Cider A, Schaufelberger M, Sunnerhagen KS, Andersson B. Hydrotherapy—a new approach to improve function in the older patient with chronic heart failure. Eur J Heart Fail 2003;5:527–35.
[9] Austin J, Williams R, Ross L, Moseley L, Hutchison S. Randomised controlled trial of cardiac rehabilitation in elderly patients with heart failure. Eur J Heart Fail 2005;7:411–7.
[10] O'Keeffe ST, Lye M, Donnellan C, Carmichael DN. Reproducibility and responsiveness of quality of life assessment and six minute walk test in elderly heart failure patients. Heart 1998;80:377–82.
[11] Boxer RS, Wang Z, Walsh SJ, Hager D, Kenny AM. The utility of the 6-minute walk test as a measure of frailty in older adults with heart failure. Am J Geriatr Cardiol 2008;17:7–12.

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Alice in Wonderland of statin therapy for small abdominal aortic aneurysm

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In a recent meta-analysis by the RESCAN collaborators [1] of individual data collated from 15,475 people under follow-up for a small (3.0–5.4 cm in diameter) abdominal aortic aneurysm (AAA) in 18 studies, no single drug used for cardiovascular risk reduction (angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blockers, statins/lipid-lowering drugs, antiplatelet agents, and any antihypertensive drug) had a major effect on the growth of small aneurysm. After adjustment for potential confounding, the pooled meta-analysis estimate (4621 patients from 6 studies) was no longer statistically significant for statins/lipid-lowering drugs (effect estimate [mm/year], −0.205; standard error, 0.132; $p = 0.121$). Several previous meta-analyses [2–6] of a small number (≤ 7) of observational comparative studies, however, suggest that statin therapy is associated with less growth rates in patients with small AAA. Further, our most recent pooled analysis [7] of 11 studies also demonstrated a significant reduction in AAA growth rates among patients assigned to statin therapy versus no statins (standardized mean difference, −0.420; 95% confidence interval [CI], −0.651 to −0.189; $p<0.001$). To determine whether statin therapy is associated with less growth rates of small AAA, we combined adjusted data for growth rates from high-quality observational comparative studies identified by comprehensive search with those from the individual patient data meta-analysis by the RESCAN collaborators [1].

All randomized controlled trials and high-quality observational comparative studies of statin therapy enrolling patients with small AAA were identified using 2-level search strategy. First, public domain databases including MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched through June 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. 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 small (<55 mm in diameter) AAA; patients were assigned to statin therapy versus placebo or no statins; and outcomes included adjusted data on aneurysm growth rates. Data regarding detailed inclusion criteria, duration of follow-up, and AAA growth rates (adjusted growth rates [mm/year] or adjusted mean differences [MDs] of growth rates [mm/year]) were abstracted from each individual study. On the other hand, adjusted effect estimates (mm/year) for statins/lipid-lowering drugs were extracted from 6 studies (Gävle [8], Leeds [unpublished], PIVOTAL [9], Propanolol [10], UKSAT [11], and Western Australia [12]) included in the meta-analysis by the RESCAN collaborators [1].

Study-specific estimates were combined using inverse variance-weighted averages of logarithmic MDs in the fixed- and random-effects model. Between-study heterogeneity was analyzed by means of standard χ^2 tests. Where significant statistical heterogeneity was identified, the random-effects estimate was used preferentially as the

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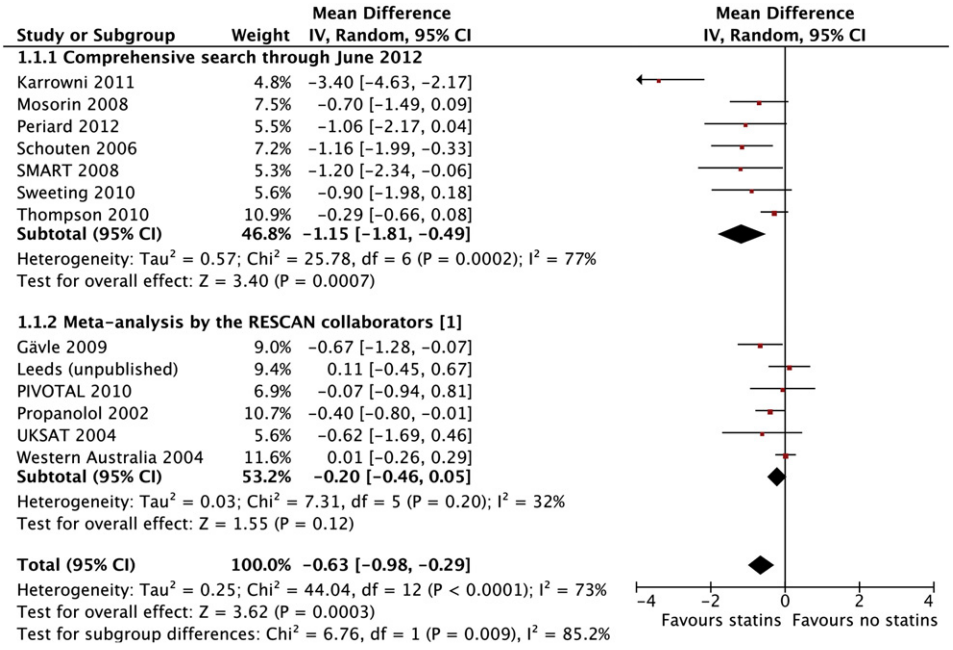

Fig. 1. Forrest plot of aneurysm growth rates (mm/year) among patients with small abdominal aortic aneurysm assigned to statin therapy versus no statins. CI, confidence interval; IV, inverse variance.

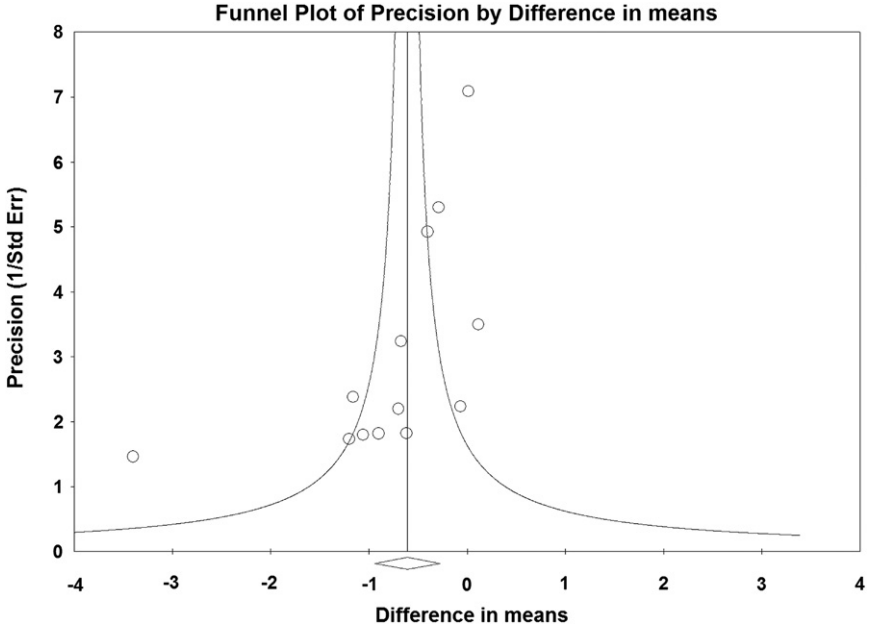

Fig. 2. Funnel plot without trim and fill. Open circles and an open rhombus denote identified studies and their summary measure, respectively.

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 MD estimates for the remaining studies. Publication bias was assessed graphically using a funnel plot and mathematically using the Begg and Mazumdar adjusted rank-correlation [13] and Egger linear regression test [14]. We also performed the Duval and Tweedie nonparametric "trim and fill" procedure [15] to further assess the possible effect of publication bias in our meta-analysis. This method considers the possibility of hypothetical "missing" studies that might exist, imputes their MDs, and recalculates a pooled MD that incorporates the hypothetical missing studies as though they actually existed. All analyses were conducted using Review Manager version 5.1 (Nordic Cochrane Centre, Copenhagen, Denmark) and Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ).

Our updated comprehensive search identified no randomized controlled trial and 7 high-quality observational comparative studies (reporting adjusted data on AAA growth rates) [16–22]. In total, the present meta-analysis included data on 9268 patients with small AAA assigned to therapy with statins and no statins from 13 studies (our identifying 7 studies plus the 6 studies included in the meta-analysis by the RESCAN collaborators [1]). Five of the 13 individual studies