

## LETTERS TO THE EDITOR

## Regarding "Growth predictors and prognosis of small abdominal aortic aneurysms"

We read with great interest the article by Schlösser et al<sup>1</sup> who concluded that lipid-lowering drug (statins) treatment and initial abdominal aortic aneurysms (AAA) diameter appeared to be independently associated with lower AAA growth rates. Statin therapy reduces the progression of atherosclerosis and improves clinical outcomes in cardiovascular disease, and there is evidence from a number of studies to suggest that statins may influence aneurysm growth rate presumably via pleiotropic effects.<sup>2</sup> A prospective randomized study would be justified on the basis of preliminary findings, but it would hardly be feasible because the use of statins is currently indicated in a growing number of patients with AAA for the management of hypercholesterolemia as well as of coronary and peripheral vascular disease.<sup>3</sup> Therefore, we herein performed a meta-analysis of currently available observational clinical studies of statin therapy for reduction of AAA growth.

Our comprehensive search identified three observational clinical studies (including the study by Schlösser et al)<sup>1,3,4</sup> of statin therapy vs control (no statin) enrolling patients with AAA. We excluded the study by Sukhija et al,<sup>5</sup> because no growth rates but absolute growth was reported. In the retrospective study by Mosorin et al,<sup>3</sup> 121 patients with AAA of at least 30 mm undergoing ultrasonographic scan surveillance for at least 1 year (serial examinations at 3- to 12-month intervals) were included. In the analysis by Schouten et al,<sup>4</sup> 150 patients under surveillance with a follow-up for aneurysm growth of at least 12 months and a minimum of 3 diameter evaluations were retrospectively included. In total, our meta-analysis included data on 418 patients with AAA assigned to statin therapy (n = 156) or control (n = 262). In the studies by Schlösser et al<sup>1</sup> and Schouten et al,<sup>4</sup> adjusted mean differences (MDs) of growth rates (mm/year) (ie, growth rates in the statin group minus those in the control group) and 95% confidence intervals (CIs) were reported. For the study by Mosorin et al,<sup>3</sup> data regarding crude growth rates in both the statin and control groups were used to generate MDs and 95% CIs. Study-specific estimates were combined using inverse variance-weighted averages of logarithmic MDs in a random-effects model. Between-study heterogeneity was analyzed by means of standard  $\chi^2$  tests. Pooled analysis of the three studies demonstrated a statistically significant 1.00 mm/year reduction in growth rate with statin therapy relative to control (MD, -1.00; 95% CI, -1.54 to -0.47;  $P = .0002$ ) (Fig). There was no between-study heterogeneity of results ( $P = .71$ ).

The results of our analysis suggest that statin therapy may reduce AAA growth rates by 1.00 mm/year, which reinforces

those of the study by Schlösser et al.<sup>1</sup> The reduction in aneurysm growth by statin therapy may prevent aneurysm repair or rupture. If a randomized placebo-controlled trial is hardly possible,<sup>1</sup> more observational studies and a meta-analysis of them are needed to confirm our results.

Hisato Takagi, MD, PhD  
Hideaki Manabe, MD  
Norikazu Kawai, MD  
Shin-nosuke Goto, MD  
Takuya Umemoto, MD, PhD

Department of Cardiovascular Surgery  
Shizuoka Medical Center  
Shizuoka, Japan

## REFERENCES

- Schlösser FJ, Tangelder MJ, Verhagen HJ, van der Heijden GJ, Muhs BE, van der Graaf Y, et al. Growth predictors and prognosis of small abdominal aortic aneurysms. *J Vasc Surg* 2008;47:1127-33.
- Baxter BT, Terrin MC, Dalman RL. Medical management of small abdominal aortic aneurysms. *Circulation* 2008;117:1883-9.
- Mosorin M, Niemela E, Heikkinen J, Lahtinen J, Tiozzo V, Satta J, et al. The use of statins and fate of small abdominal aortic aneurysms. *Interact Cardiovasc Thorac Surg* 2008;7:578-81.
- Schouten O, van Laanen JH, Boersma E, Vidakovic R, Feringa HH, Dunkelgrün M, et al. Statins are associated with a reduced infrarenal abdominal aortic aneurysm growth. *Eur J Vasc Endovasc Surg* 2006;32:21-6.
- Sukhija R, Aronow WS, Sandhu R, Kakar P, Babu S. Mortality and size of abdominal aortic aneurysm at long-term follow-up of patients not treated surgically and treated with and without statins. *Am J Cardiol* 2006;97:279-80.

doi:10.1016/j.jvs.2008.07.065

## Reply

We would like to thank Dr Takagi and his colleagues for their thoughtful comments and additive meta-analysis on our article about growth predictors and prognosis of small abdominal aortic aneurysms (AAA). Their meta-analysis reinforces the conclusion that statins are associated with lower AAA growth rates. The relatively large number of patients included allowed for a more precise estimate of the effect of statins on AAA growth rates.

Review: Statins for abdominal aortic aneurysm  
Comparison: 01 Statins vs control  
Outcome: 01 Growth rate (mm/y)

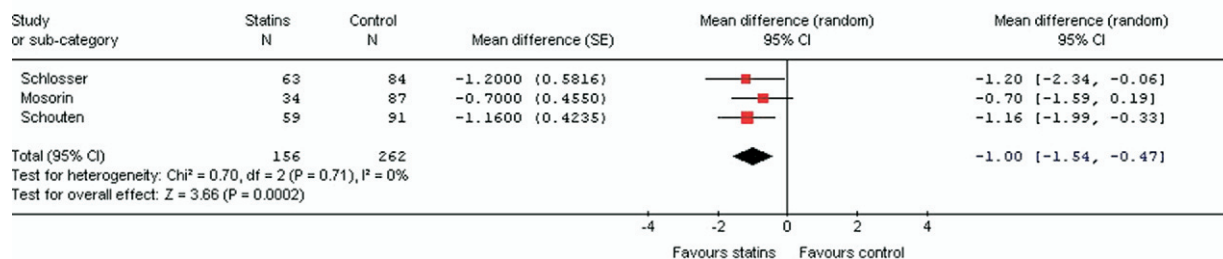


Fig. Mean differences of aneurysm growth rate and meta-analysis. SE, Standard error; CI, confidence interval.

We would like to emphasize that, according to American College of Cardiology/American Heart Association (ACC/AHA) guidelines, standard medical therapy of each patient with peripheral atherosclerotic disease should include statins, if no contraindication is present.<sup>1</sup> Importantly, as shown by the Reduction of Atherothrombosis for Continued Health (REACH) registry, statins are underused in this patient population.<sup>2</sup> Besides the attenuation of AAA growth, statin treatment improves long-term cardiac outcome of patients after major vascular surgery, which is the predominant cause of late mortality. In addition, statins also have a beneficial effect on the early postoperative outcome. A meta-analysis by Hindler et al showed that statin treatment was associated with a 59% reduction in overall short-term mortality after vascular surgery (1.7% vs 6.1%;  $P = .0001$ ),<sup>3</sup> confirmed by the study of Feringa et al.<sup>4</sup> In this study, statin users aged  $\geq 65$  years experienced a reduced hospital mortality and long-term mortality after major non-cardiac vascular surgery. In addition to survival benefits, statins are also associated with a reduction in postoperative infections,<sup>5</sup> improved recovery from acute kidney injury after major vascular surgery,<sup>6</sup> and improved preservation of renal function after suprarenal aortic cross-clamping.<sup>7</sup>

We agree with the authors that a placebo-controlled randomized trial cannot be justified anymore due to the continuously growing evidence in literature of beneficial effects of statins in patients with vascular diseases, including AAAs. Future randomized trials may, however, improve treatment strategies by comparing the effect of various statin therapies and treatment targets on AAA growth rates and clinical outcomes in patients with AAA.

Felix J. V. Schlösser, MD  
Marco J. D. Tangelder, MD, PhD  
Frans L. Moll, MD, PhD

Department of Vascular Surgery  
University Medical Center Utrecht  
Utrecht, The Netherlands

Don Poldermans, MD, PhD

Department of Anesthesiology  
Erasmus Medical Center  
Rotterdam, The Netherlands

## REFERENCES

1. Hirsch AT, Haskal ZJ, Hertzner NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients with Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *J Am Coll Cardiol* 2006;47:1239-312.
2. Röther J, Alberts MJ, Touzé E, Mas JL, Hill MD, Michel P, et al. Risk factor profile and management of cerebrovascular patients in the REACH Registry. *Cerebrovasc Dis* 2008;25:366-74.
3. Hindler K, Shaw AD, Samuels J, Fulton S, Collard CD, Riedel B. Improved postoperative outcomes associated with preoperative statin therapy. *Anesthesiology* 2006;105:1260-72.
4. Feringa HH, Bax JJ, Karagiannis SE, Noordzij P, van Domburg R, Klein J, et al. Elderly patients undergoing major vascular surgery: risk factors and medication associated with risk reduction. *Arch Gerontol Geriatr* 2008 Jan 3 [Epub ahead of print].
5. Coleman CI, Lucek DM, Hammond J, White CM. Preoperative statins and infectious complications following cardiac surgery. *Curr Med Res Opin* 2007;23:1783-90.
6. Welten GM, Chonchol M, Schouten O, Hoeks S, Bax JJ, van Domburg RT, et al. Statin use is associated with early recovery of kidney injury after vascular surgery and improved long-term outcome. *Nephrol Dial Transplant* 2008 Jul 15 [Epub ahead of print].
7. Schouten O, Kok NF, Boersma E, Bax JJ, Feringa HH, Vidakovic R, et al. Effects of statins on renal function after aortic cross-clamping during major vascular surgery. *Am J Cardiol* 2006;97:1383-5.

doi:10.1016/j.jvs.2008.07.066

## Regarding "Statins are independently associated with reduced mortality in patients undergoing infrainguinal bypass graft surgery for critical limb ischemia"

Do statins save lives in patients undergoing infrainguinal bypass surgery for critical limb ischemia? Schanzer et al<sup>1</sup> found that the use of statin drugs was associated with a significant 1-year survival benefit in patients undergoing surgical bypass grafting for critical limb ischemia. However, the authors did not appear to consider baseline cholesterol, as hypercholesterolemia is strikingly related to statin use.<sup>1</sup>

It is well known that among hospitalized disabled older adults, elevated levels of cholesterol are associated with an increased rate of recovery from disability in basic activities of daily living.<sup>2</sup> On the other hand, in surgical patients, hypocholesterolemia is a strong predictor of in-hospital death, nosocomial infections, and length of hospital stay.<sup>3</sup> Furthermore, in patients undergoing general surgery, a low total cholesterol level has been shown to be strongly associated with death after 2 years after discharge from the hospital.<sup>4</sup>

Curiously, a subgroup analysis of the Heart Protection Study focusing on patients with peripheral artery disease<sup>5</sup> failed to consider mortality data by combining deaths with aneurysm repairs. They found a small increase among those randomized to simvastatin for this combined end point.<sup>5</sup> Therefore, it is highly plausible that in the study by Schanzer et al,<sup>1</sup> statin use selected the healthy statin user or unselected the unhealthy low-cholesterol patient.

Luca Mascitelli, MD

Medical Service  
Comando Brigata alpina "Julia"  
Udine, Italy

Francesca Pezzetta, MD

Cardiology Service  
Ospedale di Tolmezzo  
Tolmezzo, Italy

Mark R. Goldstein, MD

Fountain Medical Court  
Bonita Springs, Fla

## REFERENCES

1. Schanzer A, Hevelone N, Owens CD, Beckman JA, Belkin M, Conte MS. Statins are independently associated with reduced mortality in patients undergoing infrainguinal bypass graft surgery for critical limb ischemia. *J Vasc Surg* 2008;47:774-781.