Dear Editor,

We read the meta-analysis by Takagi et al.1 with interest. Unfortunately, the conclusion that statins reduce AAA expansion is still not justified by the data.

The problem, as with our analysis widely quoted in the paper,2 is that the study quality was poor with small patient numbers in individual studies. Study results were open to confounding from multiple comorbidities and polypharmacy in AAA patient groups. Heterogeneity in the authors’ analysis was highly significant (adjusted from \( P < 0.0001 \) to \( P = 0.005 \)), with a significant variation between expansion rate results suggesting bias. Adjusting confounded or biased data and performing meta-regression simply produce further inaccurate results without correcting the underlying problem. Meta-analysis is only as good as the trial data entered.3

For these reasons we based our conclusion on sensitivity analysis rather than the meta-analysis of all trials which found in favour of the statin group.4 Adding the ‘high quality’ trial (Karrowni 2011) published since our analysis pushes our high quality sensitivity analysis result into significance (SMD \(-0.25\), \( P = 0.04\), Heterogeneity \( P < 0.0001 \)) but still gave a non significant result from large volume (>200 patients total) sensitivity analysis (SMD \(-0.20\), \( P = 0.07\), Heterogeneity \( P = 0.006 \)), highlighting how brittle meta-analysis really is when using small individual datasets.

A more definitive attempt to answer this question can only be made by adjusted re-analysis of pooled raw data from these studies or a high quality RCT.

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Reply to ‘Comment on: ‘Effects of Statin Therapy on Abdominal Aortic Aneurysm Growth: A Meta-analysis and Meta-regression of Observational Comparative Studies’

Dear Editor,

We would like to greatly acknowledge the comment by Twine and Williams on our recently published meta-analysis.1 In a more recent (after our performing the meta-analysis1) meta-analysis by the RESCAN collaborators2 of individual data collated from people under follow-up for a small (3.0–5.4 cm in diameter) abdominal aortic aneurysm (AAA), 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; \( P = 0.121 \)) after adjustment for potential confounding. The most recently, we3 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.4 Pooled analysis of 13 studies (our identifying 7 studies plus the 6 studies included in the meta-analysis by the RESCAN collaborators)5 demonstrated a statistically significant 0.63 mm/year reduction in AAA growth rates with statin therapy in the random-effects model (95% confidence interval [CI], \(-0.98 \) to \(-0.29 \) mm/year; \( P \) for effect = 0.0003; \( P \) for heterogeneity < 0.0001). Significant statistical between-study heterogeneity of the study-specific estimates may be due to the result by Karrowni et al.4 demonstrating a probably excess benefit of statin therapy (mean difference [MD] of growth rates, \(-3.40 \) mm/year; 95% CI, \(-4.63 \) to \(-2.17 \) mm/year). Even though the result by Karrowni et al.4 was eliminated in sensitivity analyses excluding individual studies one at a time, combining the remaining 12 studies (there was minimal between-study heterogeneity \( P = 0.05 \)) generated an attenuated but still statistically significant result favoring statin therapy (random-effects MD, \(-0.42 \) mm/year; 95% CI, \(-0.66 \) to \(-0.18 \) mm/year; \( P \) for effect = 0.0007).3 Thus, the evidence of the benefit of statin therapy for AAA growth is likely compelling and robust.

REFERENCES
Comment on: ‘Factors Influencing Wound Healing of Critical Ischaemic Foot after Bypass Surgery: Is the Angiosome Important in Selecting Bypass Target Artery?’

Dr. Azuma and his colleagues’ paper categorized the revascularization of an angiosome as direct or indirect. This fails to recognize the 3-dimensional anatomy of angiosomes that includes arterial—arterial connections in the foot and ankle between the arteries feeding the angiosomes. By failing to recognize the critical role those connections play in revascularization, the paper cannot accurately judge the quality of revascularization of a given angiosome.

In counter-distinction, Varela’s paper recognizes that fact by describing 3 types of revascularization of a given angiosome: direct, indirect through arterial—arterial connections and indirect. They found no significant difference in healing and limb salvage rates between the directly revascularized group and the indirectly revascularized via arterial—arterial connection(s) group. On the other hand, there was a significant difference between both groups when compared to the indirectly revascularized group without arterial—arterial connections.

I recommend adopting the Varela’s categorization of revascularization whenever using the angiosome concept to more accurately evaluate the quality of revascularization, limb salvage rates and wound healing outcomes. The first would be the direct revascularization (DR) of the artery feeding a given angiosome. The second would be the indirect revascularization (IRc) of the artery feeding a given angiosome via arterial—arterial connections. The third would be indirect revascularization (IR) where the artery feeding the angiosome remains occluded. In this instance, healing will depend on whether the “choke” vessels between angiosomes eventually open up or not.

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Response to Letter to the Editor: ‘Factors Influencing Wound Healing of Critical Ischaemic Foot after Bypass Surgery: Is the Angiosome Important in Selecting Bypass Target Artery?’

Dear Editor,

As the author of the letter mentioned, the arterial connection between angiosomes is crucial to determine the efficacy of angiosome-indirect revascularisation. However, it was not easy to classify IRc (indirect revascularisation with arterial—arterial connection) and IR (indirect revascularisation without arterial—arterial connection) because of the following reasons. (1) Preoperative arterial images such as DSA from the femoral artery, sometimes failed to show a detailed arteriogram in a severely ischaemic foot because a sufficient amount of contrast agent could not reach the foot. (2) Angiography after the establishment of a bypass could reveal the precise image of the foot. However, differentiating between IRc and IR was still difficult, because connecting arteries were also involved in arterial disease to various degrees or the connection was composed of very fine arterioles, and it was difficult to determine whether the network could contribute blood supply to the neighbouring angiosome. (3) Because the angiosome concept had not been popularised at the time of our retrospective study, the detailed three-dimensional completion angiographies were not available in many cases. (4) Angiography itself has certain limitations and cannot demonstrate the functional or haemodynamic role of the connecting circulation between angiosomes. As we mentioned in our manuscript, indocyanine green dye is utilised to intraoperatively stain the “living angiosome” in some cases to ensure that the angiosome-indirect flow through the bypass graft can contribute to feeding neighbour angiosomes.