Table. Association of statin prescription with abdominal aortic aneurysm (*AAA*) growth

First author	*Year*	*No.*	*Follow-up, years (IQR)*	*Adjusted*	*Analysis*	*Associations with statin prescription*
Sweeting[3]	2010	1701	1.9	Yes	Linear regression	None
Thompson[4]	2010	1197	3.4 (2.0-6.5)	Yes	Hierarchical	None
Ferguson[5]	2010	652	5 (3-6)	Yes	Logistic regression	None
Karlsson[a]	2009	213	NS	No	Linear regression	Reduced growth
Mosorin[a]	2008	121	3.6 ± 2.2	Yes	Linear regression	Reduced need for AAA repair
Schlosser[a]	2008	147	3.3	Yes	Linear regression	Reduced growth
Schouten[a]	2006	150	3.1 [1.1-13.1]	Yes	Linear regression	Reduced growth
Sukhija[a]	2006	130	2 ± 0.5	No	NS	Reduced growth

IQR, Interquartile range; *NS,* not stated.
[a]Article included in the meta-analysis (refer to Takagi et al[1] for citation).

focused specifically on the association of statin prescription with AAAs in the title and abstract reported reduced AAA growth in patients receiving the medication (Table). In contrast, those in which statin medication was not the primary focus found no association between statin prescription and AAA growth.[3,4]

Finally, the only study we are aware of that has reported the association of statin prescription with the development of AAAs found no evidence to support a protective effect of this medication. Forsdahl et al[6] performed ultrasound imaging at recruitment and 7 years later in 4000 individuals and reported no reduction in the incidence of AAA development in individuals prescribed statins. In fact, statin prescription was positively associated with AAA development (odds ratio, 3.77; 95% confidence interval, 1.45-9.81). The later finding may simply represent a confounding effect of trying to associate any one factor with an event.

In summary, current evidence does not support the prescription of statins to inhibit AAA expansion alone. There is good evidence for the value of statins in patients with symptomatic coronary heart and peripheral artery disease, but specific evidence that statins influence AAA expansion is lacking. Trials designed to assess the efficacy of a variety of potentially beneficial medications on AAA expansion are desperately needed, given that early surgical repair of small AAAs does not reduce mortality.[7,8]

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Regarding "Results of the randomized, placebo-controlled clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease (CASPAR) trial"

The clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease (CASPAR) investigators have examined the question of optimal antithrombotic therapy in lower extremity bypass (LEB) patients.[1] Their data suggest a benefit for the addition of clopidogrel to standard aspirin therapy in patients undergoing LEB with prosthetic, although not venous, conduits. Some additional information would help to provide context for these observations and their implications for everyday practice.

The study design specified that patients were randomized several days after completion of the operation. This introduces a potential selection bias and may limit generalizability of the result. Were some patients excluded from participation in the trial based on intraoperative findings or other factors beyond the study exclusion criteria? How representative is the study population of all patients undergoing LEB operations at these centers?

Prior studies have suggested that the mode of failure for infrainguinal prosthetic grafts is notably different than that for venous grafts.[2] Specifically, a higher surgical acuity and rate of clinical deterioration has been noted for prosthetic graft occlusion, related to the extension of thrombus into the native vessels. It would be of interest to know if the clinical presentation of graft failure in the CASPAR trial differed by treatment group and conduit type.

I take issue with a point made by the authors twice within their Discussion. Their assertion that clopidogrel reduces the failure rate of prosthetic grafts to approximate that of venous grafts is unfounded. This comparison simply cannot be made in their study in a statistically valid fashion. Patients in the CASPAR trial were not randomized to conduit; hence, it is highly likely that those patients who received venous vs prosthetic grafts differed significantly in key clinical and anatomic variables. The authors did not share the relevant characteristics of the two conduit subgroups in the report. Multiple high quality randomized trials have demonstrated the clear superiority of venous over prosthetic grafts for LEB, even in the above-knee position.[3] The implication that clopidogrel treatment might alter this established paradigm is not substantiated by their trial, and I think highly speculative.

In comparing the data from CASPAR and bypass versus angioplasty in severe ischemia of the leg (BASIL)[4] to that from North American studies such as Project or Ex-Vivo vein graft Engineering via Transfection (PREVENT) III,[5] I am struck by two persistent observations. Despite the fact that two-thirds of the patients in the CASPAR trial presented with symptoms of critical ischemia, only 25% of the LEBs performed in this study were at a tibial or pedal level. In BASIL roughly one-third of the grafts performed were infrapopliteal, whereas in PREVENT III the proportion was reversed (two-thirds were tibial/pedal). Therefore, I question if the results from these trials are relevant to patients requiring infrapopliteal bypass surgery, which appears more common in current surgical practice on this side of the Atlantic, particularly in the endovascular era. Finally, all of these trials continue to demonstrate inadequate medical therapy in LEB patients, specifically the low utilization of statins, which were associated with a beneficial effect in the CASPAR trial, as well as in PREVENT III.[6] Perhaps an intensive-dose statin trial may still be of relevance in the LEB population?

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Reply

Thank you for the opportunity to comment on Dr Conte's letter, which asks some key questions. Dr Conte comments on the randomization of patients a few days after the operation. The main purpose of this study was to examine the benefits of treatment without increasing the risk of bleeding. Although it could be argued that as thrombus formation can occur intra-operatively treatment should be started immediately, or indeed pre-surgery, no one had previously explored the use of two potent antiplatelet agents in these surgical patients. The decision was therefore taken to initiate treatment a few days after surgery to ensure hemostasis at the operation site. Patients were not excluded for reasons other than protocol exclusion criteria.

Unfortunately, the point about the site of occlusion possibly being different between prosthetic and venous grafts cannot be explored, as the graft failure endpoint did not require details of the occlusion site to be documented.

In this study, clopidogrel appeared to reduce prosthetic graft occlusion to a rate found in patients undergoing venous grafting. Dr Conte is correct, however, that as randomization to prosthetic or venous graft was not a function of this trial, these two sets of patients are not comparable. Thus, it is more correct to state that although the occlusion rate appeared to be reduced to the level seen in this trial's venous graft group, further investigation is required to confirm this finding.

Regarding the geographic inequality of distal grafts between the three trials mentioned in paragraph two, we recruited throughout Europe from one of the largest surgical trials of clopidogrel, and the distribution was as reported. It may be that in PREVENT III (Project or Ex-vivo Vein graft ENgineering via Transfection III) a selection bias for the more distal graft patients probably reflected the fact that venous grafts (studied in PREVENT III) are much preferred for the distal graft site. It is thus possible that PREVENT III had a selection bias toward the more distal grafts, rather than CASPAR (Clopidogrel and Acetylsalicylic acid in bypass Surgery for Peripheral ARterial disease) and BASIL (Bypass versus Angioplasty in Severe Ischaemia of the Leg) having a selection bias against.

The writer's observation regarding a statin trial is interesting. We have tried to garner interest from pharmaceutical companies in this hypothesis; however, it would necessitate bringing all patients onto treatment and then providing more aggressive treatment to the "active group." The numbers required for such a study apparently seemed prohibitive to the companies. Interestingly, after our recent study of a gene therapy in clopidogrel, similar global statin treatment rates were observed 5 years on from the CASPAR trial.[1] This reflects the fact that peripheral artery disease remains the poor man of cardiovascular disease: underdiagnosed and undertreated.

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Temperature measurements for dose-finding in steam ablation

We very recently demonstrated the safety and efficacy of steam ablation for varicose veins in sheep and humans in a pilot study.[1] The effectiveness of endovenous thermal ablative treatments (using laser, radio frequency of steam) depends primarily on the amount of energy delivered to the venous wall.[2,3] Previously, it was