Response to Letter from Prof. Legemate Regarding “Number needed to treat: analyzing of the effectiveness of thoracoabdominal aortic repair” by Miller et al.

We thank Professor Legemate for his comments regarding the paper by Miller et al., but feel we must respond to his criticism of the ESVS’s and the EJVES’s decision to accept the paper for presentation and publication. With regard to the ESVS meeting, each submitted abstract is scored blindly by up to six people who are either members of the EJVES Editorial Board or EJVES reviewers with a good ‘track record’. As Miller’s abstract was scored among the top 35 submissions, it was accepted for oral presentation. The degree to which an abstract reflects the accompanying paper varies as does the skill of those that write the abstracts. However, I question whether a more elaborate process, perhaps involving submission of an extended abstract or the full paper, is actually feasible, when picking out the approximately the top 10% for presentation. Concerning acceptance for the journal of papers presented at annual meeting, they are sent to three reviewers the same as any other paper submitted for the journal. The explicit critique raised by Prof. Legemate on the use of historic data and the lack of details regarding survival data, was also raised by the reviewers. The paper was accepted upon revision, as I felt data represented the best available. Here I would like to emphasise, that the decision of accepting a paper for the journal, is with the editor alone.

Neither the board nor the reviewers decide—they advise.

I thank Prof. Legemate for drawing the attention to these selection processes and excuse the delayed response.

T.V. Schroeder
Department of Vascular Surgery RK, Rigshospitalet 3111, Blegdamsvej 9, 2100 Copenhagen, Denmark
E-mail address. tschroeder@dadlnet.dk

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Prof. Legemate identifies the use of remote historical controls, whose characteristics are divergent in several ways from our population, as a fundamental methodological flaw, which renders our findings ‘both misleading and meaningless’. We considered the issues of historicity and match at length before we submitted the abstract, and we debated this point with commentators from the audience in Dublin and with reviewers of the manuscript in the publication process. We freely admit that the match with our cohort is less than ideal, but we reiterate our point that the study of Bickerstaff and colleagues represents the best evidence we will ever have about the natural history of thoracic/thoracoabdominal aortic aneurysm.

Fundamentally, Prof. Legemate’s criticism is about quality of evidence, and it is based on the generally accepted evidence-based medicine doctrine that clinical trials represent the ultimate in clinical research evidence. This is generally true, but is not so in this case.

Watchful waiting clinical trials in vascular surgery are different than the kinds of clinical trials that evidence-based guidelines hold in highest esteem. The difference is that the natural history of aortic aneurysms is widely enough understood that equipoise is disrupted when aneurysms reach a certain threshold, and surgical treatment—the treatment being studied—is extended to patients in the non-surgical group. That is to say, vascular surgery trials are never run out to the bitter end (e.g. Lederle). Crossover triggers involve aneurysm size and rate of expansion, which have been shown to increase risk of rupture, and the crossovers are used for ethical, rather than scientific, reasons. How have size and rate of expansion been shown to increase risk? By observational natural history studies, such as the one we used for our comparison. Therefore, we have clinical trials—which reside at the top of the evidence hierarchy—that have crossover rules based on ‘impure’ observational data. It is a peculiar irony that, when we compute number needed to treat using the kind of data that force crossover to surgery in clinical trials, we are taken to task for not using data from clinical trials!
In the strictest sense, crossover to surgery in these trials should be considered a failure of medical therapy. If trials such as the VA study estimated event-free survival following initial treatment, the 5-year failure rate for medical therapy would be greater than 70%. Yet the trials are presented as straightforward intent-to-treat designs, and consider crossover to be an incidental occurrence rather than a treatment failure. What we have learned more than anything is that small aneurysms follow the same trajectory as large ones. Only the rate of expansion is different. The vast majority of them get worse, and they have been shown (in clinical trials) not to respond to medical management.

Clinical trials, therefore, are not the appropriate best evidence for outcome in this paradigm, because clinical trials are not allowed to proceed to outcome. Watchful waiting clinical trials are informed by the observational data that underlie their conversion rules. In this particular situation, it is an appeal to clinical trials as the highest standard of evidence for outcome, rather than the use of scrupulously gathered population-based observational data, which is ‘misleading and meaningless’.

Prof. Legemate’s denunciation of our article as something that should never have been published underscores the importance of not allowing evidence-based doctrine to become dogma. Rather, challenges to dogmatic thinking are exactly the reason why controversial material must be published. We should resist the temptation to cut every cookie mindlessly into the same shape, but instead should think about what study designs mean. Randomized clinical trials are wonderful tools most of the time, and it is tempting to argue that no observational data are ever pure enough to inform clinical practice. But uncritical adherence to any kind of guidelines, evidence-based or otherwise, is a recipe for bad practice. Clinical trials only make sense in a context in which their findings can be applied meaningfully to the actual clinical situation. Evaluating the effect of thoracoabdominal aortic repair on survival compared to the natural history of the disease is not—and will never be—one of those contexts.

C.C. Miller III*  
H.J. Safi

Department of Cardiothoracic and Vascular Surgery, University of Texas Medical School at Houston, 6410 Fannin Street, Suite 450, Houston, TX 77030, USA

E-mail address. charles.c.miller@uth.tmc.edu

*Corresponding author.

References


We found the paper by Hobbs and colleagues interesting. It provides yet more data on the risks of peripheral vascular surgery. We have some comments to make which might however temper their conclusions. The authors conclude that over a third of their patients that underwent bypass surgery for critical limb ischaemia sustained silent myocardial injury. Their conclusion is based upon their findings of elevated cardiac troponin (cTnI). They also assert that CK-MB and ECG significantly underestimate the incidence of myocardial injury.

Cardiac troponin is currently the preferred biomarker of acute myocardial infarction (MI). Unfortunately, elevation of cTnI can be detected in a variety of conditions other than myocardial ischaemia. The authors did not appear to exclude patients with known causes of cTnI elevation, such as acute coronary syndrome, myopericarditis, cardiomyopathy, pulmonary embolism, heterophile antibodies, trauma and dialysis. Indeed, recent evidence indicates that rhabdomyolysis patients may have raised cTnI. Causes of rhabdomyolysis include post-operative,