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EDITORIAL: FOR DEBATE

Reply to "The VOYAGER PAD Trial in Surgical Perspective: A Debate"

We thank the editors of the *EJVES* for the opportunity to respond to the valuable comments on our editorial[1] put forward by Anco Vahl *et al.*[2] We agree with their statement that the VOYAGER PAD trial is a landmark trial, as it represents the largest ever published cohort on antithrombotic therapies in patients receiving invasive treatment for peripheral artery disease (PAD), both endovascular and surgical. The efficacy of rivaroxaban added to aspirin was associated with a strong absolute benefit for these patients, while the incidence of bleeding was low, with no significant increase in fatal bleeding or post-procedural bleeds in patients requiring intervention.[3]

The authors criticise our assumption, that "based on the COMPASS trial, rivaroxaban is recommended for secondary prevention of cardiovascular events in several guidelines, including the 2013 ESC guideline", as well as the 2020 European Society for Vascular Surgery (ESVS) guideline for the treatment of acute limb ischaemia (ALI). Although we did not write this text as mentioned, we admit that we incorrectly referred to the 2013 European Society of Cardiology (ESC) guideline. However, the mentioned ESVS guideline highlights this dual pathway treatment, as it states the following in the chapter on post-operative medication: "The combination of low dose DOAC and low dose aspirin, as in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, has not primarily been investigated after ALI. However, in patients with stable PAD, an overall benefit from receiving rivaroxaban 2 × 2.5 mg plus aspirin 100 mg was demonstrated. A small subgroup of patients within this study who had ALI also had a marked reduction in amputation and mortality rate. Although the COMPASS trial was positive for patients with ALI, this was not the primary end point, and further research with a focus on ALI is needed".[4] This subgroup was published by Anand *et al.*[5] In addition, three other guidelines have mentioned this drug combination within their recommendations.[6–8] VOYAGER PAD now adds further supportive data, including a significant reduction in the primary outcome that includes ALI. Because these data are recent, they have not yet been evaluated by guideline writers.

Vahl *et al.* refer to the CAPRIE trial,[9] which was not a dedicated PAD trial and did not primarily include post-revascularisation patients. They assumed that the relative risk reduction in this trial would be 9% *vs.* 1%, as in VOYAGER. In fact, CAPRIE showed an 8.7% relative risk reduction for major adverse cardiovascular events (MACE) and no benefit for limb outcomes, whereas VOYAGER showed a 15% relative risk reduction (approximately double that in CAPRIE), including MACE and limb outcomes. In addition, CAPRIE only included stable patients. Conversely, VOYAGER PAD was an adjunct to a revascularisation trial. It is also notable that CAPRIE was conducted before the routine use of statins and other medical therapies, was a monotherapy trial, and, in contrast to the VOYAGER PAD trial, there was no amputation benefit.

However, it is correct that the main driver of the VOYAGER PAD trial was a reduction in ALI. The definition of ALI was the same as that of the TRA2<P-TIMI 50 trial[10] and the EUCLID trial,[11] and both studies have clearly shown events with very serious outcomes associated with long hospitalisations (median ∼8 days), high rates of amputation (∼17%), and ∼15% dead or unable to live independently after an ALI presentation. We therefore disagree that these are not important outcomes.

The comment that a reduction in ALI was not significant in critical limb ischaemia (CLI) is not true. This is a subgroup and there was no heterogeneity within the overall cohort, meaning that the benefit was the same in those with and without CLI. In fact, the number needed to treat (NNT) for CLI was even more favourable owing to the fact that risk and net outcomes were reduced. However, we are grateful that the high number of claudicants in this trial was mentioned in their comment. We think that this is an important finding of VOYAGER (and other recent trials) that after lower extremity revascularisation for claudication the risk of developing ALI is greatly increased.

Although we agree that we need more long term data concerning secondary prevention, we think that, with three years of follow up, the VOYAGER PAD trial compares favourably with other recent trials. For example, the CAPRIE trial, which the authors cite, had a mean duration of 1.91 years and most studies of aspirin for secondary prevention were approximately two years in length. In conjunction with the COMPASS data, with the same drug regimen in stable patients with PAD, we believe there is reasonable evidence to mention this drug combination as a beneficial long term secondary prevention treatment strategy.

We agree that aspirin monotherapy has demonstrated limited benefit in the protection of cardiovascular events for patients with PAD, including those following surgical reconstruction. Moreover, the authors state that clopidogrel is protective after surgery. With respect to the CASPAR trial,[12] we do not agree with this statement: CASPAR randomised patients after surgical lower extremity revascularisation to clopidogrel *vs.* placebo. Clopidogrel was not able to reduce events, while it was associated with

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increased bleeding events. This is a key reason why clopidogrel was not favoured over aspirin as a primary antithrombotic monotherapy in the abovementioned guidelines. In addition, the benefits of rivaroxaban in this population are consistent, regardless of background clopidogrel use.

Finally, the Vahl *et al.*[2] state that cost effectiveness studies are needed, as in the Netherlands, in particular, rivaroxaban is more expensive than clopidogrel. This is certainly true, although those studies always have a national limit. Given the high efficacy of the combination of rivaroxaban with aspirin in reducing cardiovascular events with fewer re-hospitalisations and redo procedures, the benefit of this new drug combination may be obvious for both patients and healthcare systems. Certainly, with an absolute risk reduction of 2.6% (NNT = 39) in the overall trial and the high cost of limb outcomes, it would seem clear that there is cost effectiveness depending on the cost in any particularly setting. Nevertheless, cost effectiveness analyses are underway in the overall trial and could be conducted in higher risk groups such as those with CLI and will, hopefully, provide additional support for the adoption of this important new therapy.

CONFLICTS OF INTEREST

Dr Debus reports receiving grants from Bayer AG, Cook LTD, and Terumo Aortic during the conduct of the study. Dr Nehler reports receiving grants from Bayer and Janssen during the conduct of the study, and from CPC Research outside of the submitted work.

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