

EDITORIAL: FOR DEBATE

The Voyager PAD Trial in a Surgical Perspective: A Debate

In a recent editorial, Debus and Nehler commented on the Voyager PAD trial,¹ which showed a clinical benefit of combined rivaroxaban 2 × 2.5 mg on top of aspirin 100 mg vs. aspirin 100 mg alone in patients after recent successful endovascular or open revascularisation for symptomatic peripheral arterial disease (PAD).² While Voyager PAD is a landmark trial, with the unique combination of a modern oral anticoagulant and platelet inhibitor, the authors may have been a little overenthusiastic in their interpretation of the trial data.

The authors state, “based on the COMPASS trial,³ rivaroxaban is recommended for secondary prevention of cardiovascular events in several guidelines, including the 2013 ESC guideline”.⁴ In fact, this European Society of Cardiology (ESC) guideline does not include a recommendation to give rivaroxaban to patients with PAD, and this is also true of the 2020 European Society for Vascular Surgery guidelines for the treatment of acute limb ischaemia (ALI).⁵ It is true that the Cardiovascular Outcomes for People Using Anti-coagulation Strategies (COMPASS) study is mentioned in the ALI guidelines; however, COMPASS did not include a subgroup analysis of patients with ALI. The guidelines state: “In patients requiring antiplatelet therapy, clopidogrel may be preferred over aspirin”.

Almost 25 years ago another landmark trial was published: the CAPRIE (Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events) trial.⁶ In CAPRIE, aspirin monotherapy was compared with clopidogrel monotherapy. Unfortunately, the editorial did not comment on the results of CAPRIE, which included almost the same patients and used the same composite endpoints but with a slightly shorter follow up time. The relative risk reduction (RRR) of the composite endpoint was 9% in favour of clopidogrel. In the Voyager PAD trial the RRR was 13%, but in Voyager the composite endpoint had more components. Applying the same components in Voyager as used in the CAPRIE trial, the RRR appears to be 1%, and this would no longer be significant.

The main driver of the clinical benefit in Voyager PAD was a reduction in ALI. Contrary to the statement in the editorial, there was no statistically significant difference in any other individual endpoint, including amputation for vascular causes. Additional rivaroxaban led to a 0.78% increase in major Thrombolysis in Myocardial Infarction (TIMI) bleeding, translating into a RR increase of 43%, which was not statistically significant ($p = .07$). On closer inspection,

the only component of the endpoint in the Voyager trial with a significant reduction was ALI (32%), with an absolute risk reduction of 2.2%. So, for intervention reasons the Voyager PAD results might be interesting, with a number needed to treat of 45 in order to prevent ALI. However, the problem is that the applied definition of ALI is very broad, defined as a clinical history and presentation consistent with a sudden significant worsening of limb perfusion. Moreover, 76% of patients in Voyager were treated for claudication, which is not likely to lead to ALI.

It is even more confusing that the reduction in composite endpoint was significant in patients treated for claudication and not for critical limb ischaemia, and that in patients treated by endovascular revascularisation there was no benefit vs. a significant benefit after surgical revascularisation. Which of the components of the composite endpoint were the drivers of these differences is not reported, and a detailed subgroup analysis is needed to define those patients who may benefit most from the Voyager regimen.

For secondary prevention reasons the combination of rivaroxaban and aspirin has not yet been proven. Furthermore, as we already know based on other observational studies, aspirin monotherapy is not sufficient for patients with PAD, for patency of interventions like bypass surgery,⁷ or for secondary prevention reasons. Systematic reviews have already concluded that aspirin monotherapy scores worse than other regimens, and that we need something more protective, such as clopidogrel.^{8–10}

Unfortunately, the choice of aspirin as comparator treatment in the Voyager PAD trial has been suboptimal. Clopidogrel, which is a more potent drug than aspirin for secondary prevention and is endorsed by current guidelines, would have been the more obvious choice.¹¹

Last, but not least, at this time rivaroxaban is far costlier (in the Netherlands, eight times more) than clopidogrel. Another potential problem is that, based on the results of the Voyager trial, patients have to take three tablets a day, sometimes four when a proton pump inhibitor is used, compared with only one tablet when using clopidogrel. This may affect patient compliance. Cost effectiveness analyses are needed to define the position of adding rivaroxaban to standard care for prevention of cardiovascular events in patients with PAD, with or without revascularisation.

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