

EDITORIAL

Navigating the Passage for Better Understanding and Prognosis for Acute Limb Ischemia After Lower-Extremity Revascularization

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Antithrombotic treatment after lower extremity revascularization (LER) for peripheral artery disease (PAD) has been largely extrapolated from subanalyses of trials involving patients undergoing percutaneous coronary intervention, with limited PAD-specific data.¹ However, post-LER patients are at high risk of adverse limb and cardiovascular events, reflecting both a more aggressive atherosclerotic state and a higher postintervention inflammatory activity. This increased risk persists years after the procedure despite antiplatelet and statin therapy,^{2,3} which sparked increasing interest in the role of more intense antithrombotic strategies to reduce adverse outcomes without significantly increasing the risk of bleeding.⁴ The VOYAGER-PAD trial (Efficacy and Safety of Rivaroxaban in Reducing the Risk of Major Thrombotic Vascular Events in Subjects With Symptomatic Peripheral Artery Disease Undergoing Peripheral Revascularization Procedures of the Lower Extremities) provided evidence to guide post-LER antithrombotic therapy by ascertaining the safety and efficacy of dual-pathway inhibition (DPI; rivaroxaban 2.5 mg twice daily along with aspirin) versus aspirin, initiated within 10 days after revascularization in patients undergoing surgical or endovascular LER below the external iliac artery.⁵ At 3 years, the primary efficacy end point (acute limb ischemia [ALI], major amputation, myocardial infarction, ischemic stroke, or cardiovascular death) was significantly reduced with DPI versus aspirin (hazard ratio [HR], 0.85 [95% CI, 0.76–0.96]), with a nonsignificant increase in TIMI (Thrombolysis in Myocardial Infarction) major bleeding (HR, 1.43 [95% CI, 0.97–2.10]). VOYAGER-PAD was the first clinical

trial to include ALI and major amputation in the primary end point, and the trial results were driven mainly by the reduction seen in ALI.⁵

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When combined end points are interpreted, it is relevant to consider whether the individual clinical events defining this combination have clinically meaningful interpretation and that each of the individual events has similar importance to patients. The prespecified analysis of VOYAGER-PAD on the clinical course of ALI presented by Hess et al⁶ in this issue of *Circulation* is therefore important and long awaited. The article reports the results of a prespecified analysis of VOYAGER-PAD investigating the clinical course of patients experiencing ALI. The investigators examined the risk and clinical factors associated with developing ALI, the prognosis of ALI, and the effect of DPI on ALI alone among patients with PAD after LER. Previous studies show that ALI is a devastating manifestation of PAD that can rapidly progress to limb loss and disability and carries a 30-day mortality of ≈20%.⁷ Over a median follow-up of 2.3 years, 5.8% had at least 1 ALI event, with risk of ALI manifesting both in the early post-LER period and later. This suggests that ALI may be considered to be as important as myocardial infarction and stroke. In addition, randomization to DPI was associated with a 33% reduction in ALI compared with aspirin (HR, 0.67 [95% CI, 0.55–0.82]). This benefit was apparent within 30 days after randomization (HR,

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0.45 [95% CI, 0.24–0.85]) and continued over time (HR, 0.71 [95% CI, 0.57–0.88]) regardless of revascularization approach and baseline clopidogrel use.

Hess et al introduced a new combined end point, severe ALI, defined as death, major amputation for vascular causes, or peripheral revascularization and hospitalization for ≥ 7 days including at least 1 day in intensive care unit within 30 days after the initial ALI event. Although current analyses confirm the clinical relevance of including ALI in the primary outcome, this new end point definition to some extent questions the validity of combined end points. It may be challenging to argue that hospitalization of >7 days including 1 day in intensive care is as important as either being amputated or undergoing an additional revascularization. In addition, we need information on whether 1 day in the ICU was related to local practice or a high clinical dependency for intensive postoperative monitoring. Further questioning the severe ALI end point, it is interesting that the statistically significant reduction with DPI versus aspirin disappeared when hospitalization of >7 days including 1 day in intensive care was excluded (DPI, 30 of 3288 versus aspirin, 44 of 3278; $\chi^2 P > 0.09$).

At present, there are no validated prediction models to identify patients with PAD who are at risk of developing ALI. Hess et al applied multivariable regression analyses to identify risk factors associated with ALI. Individual risk factors included previous LER, current smoking, low ankle-brachial index, long target lesion length, and surgical revascularization.⁶ The methodology applied to identify these risk factors was based on stepwise selection using a *P* value criterion for covariate inclusion. However, when regression models are developed and applied, it is important to make a clear distinction between (causal) explaining and prediction.⁸ Indeed, the data at hand cannot be considered an accurate representation of the underlying construct (here the generalizability of the population). The VOYAGER-PAD data provide excellent ground for causal interpretation of the 2 treatment regimens. Yet, in the controlled (ie, constrained) environment of a trial, the data may be subject to heavy selection bias from trial eligibility criteria, which obscures a realistic context of prediction of ALI events among patients in routine care clinical practice. Therefore, identifying risk factors associated with ALI in the VOYAGER-PAD trial data may be of little use for clinicians.

Although the article by Hess et al contributes to our knowledge of risk and prognosis of ALI and the efficacy and safety of DPI in patients with PAD after LER, a key question remains. To what extent do these findings apply to patients in routine clinical care for whom the treatment is contemplated? Patients with symptomatic PAD who undergo LER represent a vulnerable subgroup of patients with multiple morbidities at high risk of complications.^{2,3} These factors are well known to influence enrollment in trials. The revascularization pro-

cedure required for inclusion in VOYAGER-PAD had to be successful, which may have induced a selection bias toward healthier and more stable patients. Furthermore, the trial excluded patients with procedural complications, those with significant ulceration, those undergoing treatment for ALI, and those with poorly controlled diabetes and hypertension. Thus, the benefit-risk balance in patients seen in clinical practice may be different. Recently, 2 studies based on French and Danish registry data have provided data on the external applicability of VOYAGER-PAD to patients encountered in routine clinical practice.^{9,10} In both studies, fewer than one-third of patients who underwent revascularization in routine practice would have been eligible in the VOYAGER-PAD trial. Compared with participants enrolled in VOYAGER-PAD, patients in routine care were older and had more severe PAD, higher bleeding risk, and generally poorer prognosis. Thus, caution is required when extending trial results to a broader patient population, but these results also confirm that eligible patients have a high risk for major adverse limb and cardiovascular events and are in great need of an effective prevention therapy. The recent 2021 European Society of Cardiology consensus on antithrombotic treatment in aortic disease and PAD states that DPI should be proposed for patients who are symptomatic or undergo LER in the absence of high bleeding risk,¹¹ thus reinforcing the need for careful benefit-risk evaluation. This underscores the urgent need for data from large, well-designed observational studies to estimate the effectiveness and safety of DPI among patients with PAD after LER in routine clinical practice to confirm benefits and risks.

The question of effectiveness and safety in patients receiving routine care remains to be answered, but the article by Hess et al calls for attention on ALI events among post-LER patients and strengthens the recommendation for DPI in these patients. Aside from the potential drawbacks highlighted here, data on ALI in VOYAGER-PAD are important for guiding optimal treatment aimed at decreasing amputations and improving prognosis after LER. Despite DPI therapy, significant risk remains, underscoring the importance of continuing preventive therapies. It is clear that DPI is no silver bullet. Control of comorbid conditions such as hyperlipidemia, diabetes, and hypertension and smoking cessation counseling remain important to mitigate the onset of and deleterious consequences associated with ALI. The high residual risk also serves as a call for further research with a focus on ALI to provide more data on long-term secondary prevention.

ARTICLE INFORMATION

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