



Editorial

Addressing Knowledge Gaps in Patients With High-Risk Peripheral Artery Disease



R. Kevin Rogers, MD, MSc^{a,b,*}, Marc P. Bonaca, MD, MPH^{a,b}

^a Section of Vascular Medicine, Division of Cardiology, University of Colorado School of Medicine, Aurora, Colorado; ^b CPC Clinical Research, Aurora, Colorado

More than 230 million individuals worldwide are estimated to have peripheral artery disease (PAD) and are at increased risk of adverse cardiovascular outcomes, with approximately 10% suffering atherothrombotic events yearly¹; however, patients with PAD are heterogeneous, with some subgroups at higher risk than others. For example, recent randomized trials evaluating revascularization strategies for patients with chronic limb-threatening ischemia (Best Endovascular vs best Surgical Therapy in patients with Critical Limb Ischemia and Bypass vs Angioplasty for Severe Ischemia of the Leg-2) observed rates of the composite of death or major adverse limb events (MALE) of 49% to 58% over approximately 3 years.^{2,3} Other characteristics that have been observed to be associated with heightened risk include prior lower extremity revascularization, including for claudication, which is associated with an approximately 4-fold higher risk of MALE,⁴ and anatomic distribution of disease.^{2,5,6} Despite these observations, a comprehensive approach to risk stratification for MALE remains an unmet need.

In this context, the Boston Femoral Artery Revascularization Outcomes (Boston FAROUT) study by Mandieka et al⁷ provides novel insights. Boston FAROUT was a retrospective cohort analysis conducted at Veterans Affairs Boston and Brigham and Women's Hospitals. The study population included all patients undergoing a first endovascular procedure of the superficial femoral artery for lifestyle-limiting claudication or chronic limb-threatening ischemia from 2003 to 2011. Patients were followed for a median of 9.3 years (IQR, 6.8-11.1 years). The primary outcome was MALE or minor revascularization. MALE was defined as major amputation, new bypass graft, or thrombolysis. Minor revascularization was defined as any repeat endovascular revascularization or common femoral endarterectomy during follow-up. Various clinical, anatomic, and procedural variables were examined for associations with outcomes. Outcomes and variables were ascertained by review of the electronic medical record or from a procedural report form.

Successful superficial femoral artery revascularization was achieved in 185 patients (232 limbs), forming the study population in

which 69 patients experienced a total of 88 events. Demographics reflected the risk profile anticipated with PAD, including age in the late 60 years, approximately half of the patients had diabetes, and about a quarter of them were active smokers. The majority (>90%) received aspirin and statin; however, almost 20% had an LDL-C >100 mg/dL. MALE or minor revascularization occurred in 88 (38%) limbs over the 9.3-year median follow-up. Twenty of these events were MALE, of which 11 were major amputations, 9 required surgical bypass, and 5 required thrombolysis/thrombectomy (some limbs had multiple end points).

Analyses incorporating patient, procedural, and anatomic features were performed to evaluate for predictors of MALE. They observed that revascularization for critical limb-threatening ischemia (CLTI) vs claudication, Black race, and LDL >100 mg/dL were all independently associated with MALE. In contrast, lesion length and smoking were independently associated with minor revascularization procedures.

These findings have several important impacts. First, they support that risk in PAD is multifactorial and associated with patient, disease, systemic, and anatomic factors as well as health equity. Improving outcomes requires a holistic and comprehensive approach to addressing all drivers of risk. Second, they demonstrate heterogeneity in the associated risk factors for different limb outcomes, supporting differing underlying pathobiological processes. Third, results support that future investigations to evaluate risk predictors for MALE should incorporate patient, disease-related, and anatomic features rather than focusing on a single factor, which likely oversimplifies risk stratification.

There are, however, several important limitations to the current analysis. It is retrospective, focused on a single anatomic segment, restricted to patients undergoing revascularization, and is a small cohort with a limited number of events that will require validation. In addition, the definition of MALE has varied across trials, and the definition used may not align with randomized trials of drug therapies or devices. Finally, the direct clinical impact is limited in that the only 2 biological factors that appear modifiable at the time of revascularization are

DOI of original article: <https://doi.org/10.1016/j.jscai.2024.102241>.

Keywords: lower extremity revascularization; peripheral artery disease; risk stratification; superficial femoral artery disease.

* Corresponding author: kevin.rogers@cuanschutz.edu (R.K. Rogers).

<https://doi.org/10.1016/j.jscai.2024.102286>

Received 8 August 2024; Accepted 12 August 2024; Available online 2 October 2024

2772-9303/© 2024 The Author(s). Published by Elsevier Inc. on behalf of the Society for Cardiovascular Angiography and Interventions Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

smoking and lowering LDL-C, both already well-established foundational components of modern medical care.

One immediate impact for all practitioners, however, is the observation that Black race is associated with worse outcomes. This finding should be a key reminder to all clinicians that health equity must be a focus for all caring for patients with PAD. For researchers, the Boston FAROUT study provides a robust example of rigorous data collection and assessment and a comprehensive approach to risk stratification; it should stand as an important step forward in the efforts to improve risk stratification and better elucidate the heterogeneous risk factors for adverse outcomes in patients with PAD.

In conclusion, the Boston FAROUT study is a welcome step forward in understanding the risk of adverse outcomes in PAD, an increasingly prevalent and highly morbid manifestation of atherosclerosis. It serves as a call to action to optimize comprehensive medical management and address health equity. It serves as an example of how we can better conduct PAD studies to gain more insight into the risk of different PAD stages (eg, asymptomatic, claudication, CLTI, prior lower extremity revascularization) and will help inform assembling the most meaningful inclusion criteria for a clinical study. Future work to build on these observations using a standardized definition of MALE will be helpful. Such a definition might include “hard” end points, such as death, major amputation, and development of acute limb ischemia, rather than repeat revascularization. Finally, ensuring optimal background medical therapy affords better insight when evaluating risk predictors and treatment strategies. Patients with PAD will benefit from more longitudinal clinical studies, like the Boston FAROUT study, that are well-designed to address enhanced risk stratification and therapies to improve limb and overall cardiovascular outcomes.

Declaration of competing interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding sources

This work was not supported by funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Fowkes FGR, Aboyans V, Fowkes FJL, McDermott MM, Sampson UKA, Criqui MH. Peripheral artery disease: epidemiology and global perspectives. *Nat Rev Cardiol*. 2017;14(3):156–170. <https://doi.org/10.1038/nrcardio.2016.179>
2. Bradbury AW, Moakes CA, Popplewell M, et al. A vein bypass first versus a best endovascular treatment first revascularisation strategy for patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal revascularisation procedure to restore limb perfusion (BASIL-2): an open-label, randomised, multicentre, phase 3 trial. *Lancet*. 2023;401(10390):1798–1809. [https://doi.org/10.1016/S0140-6736\(23\)00462-2](https://doi.org/10.1016/S0140-6736(23)00462-2)
3. Farber A, Menard MT, Conte MS, et al. Surgery or endovascular therapy for chronic limb-threatening ischemia. *N Engl J Med*. 2022;387(25):2305–2316. <https://doi.org/10.1056/NEJMoa2207899>
4. Bonaca MP, Creager MA. Antithrombotic therapy and major adverse limb events in peripheral artery disease: a step forward. *J Am Coll Cardiol*. 2018;71(20):2316–2318. <https://doi.org/10.1016/j.jacc.2018.04.001>
5. Murphy TP, Cutlip DE, Regensteiner JG, et al. Supervised exercise, stent revascularization, or medical therapy for claudication due to aortoiliac peripheral artery disease: the CLEVER study. *J Am Coll Cardiol*. 2015;65(10):999–1009. <https://doi.org/10.1016/j.jacc.2014.12.043>
6. Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med*. 2020;382(21):1994–2004. <https://doi.org/10.1056/NEJMoa2000052>
7. Mandieka E, Ohiomoba R, Sobieszczyk PS, C EA, Todoran T, Kinlay S. Long-term adverse limb events after femoral artery endovascular revascularization: the Boston FAROUT study. *J Soc Cardiovasc Angiogr Interv*. 2024;3:102241.