A Predictable Propensity
Secondary Revascularization is Associated With Further Revascularization

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The epidemiologic burden of peripheral artery disease (PAD) is remarkable with prevalence ranging from 3% to 10%, rising to 15% to 20% in patients over 70 years.1–4 Symptomatic PAD with intermittent claudication has a prevalence of up to 60% in patients over 60 years of age and the largest prospective study demonstrates an incidence of critical limb ischemia of 220 cases per 1 million population.1,5 Yet, as our awareness of this disease has grown, so too have the treatment strategies combatting it. Lower extremity bypass techniques and peripheral vascular intervention strategies have developed over time. The progress of medical therapies and the increasingly recognized importance of supervised exercise as well as ancillary wound healing techniques have allowed the clinical treatment of PAD to grow more and more sophisticated.

As more tools have become available, more complex questions have arisen regarding how to optimize the treatment of PAD. After much work, multiple national and society guidelines were established to outline interventions that target PAD.1,6 The TASC (Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease) morphological stratification of iliac and femoropopliteal lesions were implemented to guide choice of endovascular versus surgical intervention in patients with lower extremity vascular disease.1 The CLEVER trial (Claudication: Exercise Versus Endoluminal Revascularization) touted the benefits of supervised exercise even compared to peripheral vascular intervention with stenting (though without concurrent exercise therapy).7 The recent ERASE trial (Endovascular Revascularization and Supervised Exercise) built upon these findings, demonstrating greater improvements in maximum walking distance and quality of life for peripheral vascular intervention plus exercise compared with exercise therapy alone.8 With regards to critical limb ischemia, the Bypass Versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial published in 2005 regarding patients treated between 1999 and 20049 found less short-term morbidity with peripheral vascular intervention, but further analysis also demonstrated that lower extremity bypass was associated with a decreased mortality (hazard ratio [HR] 0.61 95% CI 0.50 to 0.75) compared to balloon angioplasty alone.10 This led to the American College of Cardiology and the American Heart Association (ACC/AHA) recommendation that primary lower extremity bypass is reasonable in critical limb ischemia patients with life expectancy of greater than 2 years. However, the significantly less invasive nature of endovascular intervention as well as the development of peripheral vascular intervention to include primary stenting has led many to adopt a peripheral vascular intervention-first strategy for most patients with significant lower extremity PAD. Yet with every question answered novel questions have arisen. This is particularly true regarding important clinical decisions in the subgroup that has failed initial attempts at revascularization and requires further evaluation and treatment.

In this issue of JAHA, Jones and colleagues develop a propensity analysis targeting the question of whether first treatment failure with peripheral vascular intervention or lower extremity bypass impacts the success of subsequent revascularization with lower extremity bypass.11 This examination of the impact of the distinct stages of clinical care is extremely important because management of both intermittent claudication and critical limb ischemia does not end with a first intervention. PAD and its various subtypes are chronic diseases that require life-long clinical care and have proven to often require multiple either staged or unforeseen interventions. The authors conclude that in both crude and propensity-weighted analyses, secondary lower extremity bypass was associated with significantly inferior 1-year outcomes, including major adverse limb event-free survival and reintervention or amputation-free survival. They also note that inferior outcomes for secondary lower extremity bypass were
observed regardless of whether the prior failed treatment was peripheral vascular intervention or lower extremity bypass. However, retrospective analysis, even that utilizing propensity analysis, is limited in its ability to answer the questions it targets. And rather than their results proving that first treatment failure impacts the success of a subsequent lower extremity bypass, their work simply identifies a high risk group for failure of secondary revascularization by demonstrating that those individuals who failed a first revascularization are more likely to fail a second.

A propensity score is a summation of the probability of assignment to a particular treatment contingent on specified observed baseline characteristics. The propensity score is a “balancing score” that allows for equal distribution of observed baseline covariates between distinct treatment groups, thus allowing an observational nonrandomized cohort to be studied and compared in order to answer a clinical question. Caution must be raised in the use of propensity analysis as it was implemented in this work. Propensity analysis is most commonly implemented to ask a clinical question that, at least theoretically, could have been answered in a randomized controlled fashion. In this work, it is used to compare 2 different treatments (primary versus secondary revascularization) at 2 different points in a patient’s clinical course. A patient could never be randomized to primary versus secondary revascularization and thus the use of propensity analysis in this situation is certainly atypical. The initial clinical question as well as the discussion also tackles the notion of causation. They ask if primary revascularization failure worsens outcomes after secondary revascularization with lower extremity bypass. However, this data cannot answer this question. Rather than demonstrating causation, any conclusions drawn from this work must simply be versed in terms of association. Their data demonstrate that primary revascularization failure is associated with increased rates of failure of secondary bypass. This is not unexpected and does not help with choosing primary strategies.

If propensity is deemed acceptable in this situation, it is not surprising that a patient undergoing lower extremity bypass or peripheral vascular intervention after a failed primary procedure would have a worse outcome given that this population has been “selected” out by having a primary failure. Though propensity-weighted analysis can do much towards attempting to balance compared populations, the statistical practice of propensity weighting is unable to balance a fundamental characteristic of the primary treatment failure group (that they have failed treatment). Furthermore, a methodologic weakness of the use of large registry data is the lack of anatomic, procedural, operator, and institution data which are likely important predictors of any revascularization failure (primary or secondary). Propensity which balances measured factors cannot adjust for these many unknown variables that are likely colinear with the incidence of the measured endpoints.

The secondary revascularization study group in this work is also an interesting one. Endovascular intervention can certainly be used as the secondary revascularization strategy in patients who fail primary revascularization. Current guidelines recommend choosing secondary revascularization strategies on a case-by-case basis regardless of primary revascularization modality. However, the secondary revascularization group here is exclusively treated with lower extremity bypass. That lower extremity bypass was the exclusive secondary revascularization strategy makes results drawn from this analysis less generalizable to all patients undergoing secondary revascularization. We must additionally question whether characteristics particular to this study group would further select this group from the general population that fails primary revascularization. Were particular lesion characteristics, operator availability, or primary revascularization complications particularly present in this group making these patients more likely to have lower extremity bypass versus peripheral vascular intervention as the secondary revascularization strategy? If so, these baseline characteristics could certainly run colinear to the author’s eventual outcome findings.

The outcomes are also quite interesting. There were no statistically significant differences in in-hospital mortality, MI, or ipsilateral amputation between the groups when stratified for indication for revascularization (intermittent claudication or critical limb ischemia). There were also no statistically significant differences in 1-year mortality or amputation-free survival. The only differences between the groups were in reintervention or amputation-free survival and major adverse limb event-free survival. As expected the primary endpoint driving the reintervention or amputation-free survival difference was only “freedom from any reintervention” (P<0.002) and that driving the major adverse limb event-free survival was “freedom from major reintervention” (P<0.001). Stated most clearly, this comparison thus demonstrates that compared to the primary revascularization group, the group which failed a primary revascularization strategy was associated with higher revascularization requirements after secondary revascularization. In addition to being somewhat predictable, we are also left to wonder if any other clinically relevant outcome differences existed between the groups (walking distance, pain free walking distance, quality of life measures in intermittent claudication, for instance).

The authors should be applauded for taking a complex look at revascularization strategies for PAD. They demonstrate an interest in outcomes beyond that of a single intervention. Indeed, they do demonstrate what many would suppose, that failure of an initial revascularization selects a population that may be at higher risk for failing future strategies. This speaks
to nothing if not the complexity of decision making in PAD intervention. It also raises a series of new questions. How does peripheral vascular intervention perform when compared to lower extremity bypass for secondary revascularization? How does the choice of primary intervention strategies impact secondary revascularization outcomes? Though they look exclusively at secondary lower extremity bypass patients, and though statistical significance is not calculated, it does appear from the similar Kaplan–Maier curves in their Figure 5 that the choice of primary revascularization strategy (lower extremity bypass versus peripheral vascular intervention) does not seem to affect outcomes after secondary lower extremity bypass. It is also somewhat surprising that the event-free survivals of both endpoints are relatively low.\footnote{11}

In conclusion, rates of revascularization mainly by peripheral vascular intervention are increasing\footnote{14,15} and clearly, failed primary revascularization is a predictor of reintervention in the future. However, this study does not demonstrate the appropriateness of particular primary revascularization strategies, nor does it imply that primary lower extremity bypass is superior to peripheral vascular intervention. Additionally, it does not attempt to answer which secondary strategy is superior as all patients underwent secondary lower extremity bypass. Hence, studied here is a very select population from which limited conclusions can be drawn. Clearly, patients with peripheral vascular disease are complex and require a dynamic and personalized treatment approach that accounts for comorbidities, symptoms, quality of life, and anatomic presentation. Unfortunately, many practitioners representing multiple specialties perform vascular procedures under different guidelines and without a unified governing body. Appropriateness criteria for many cardiac procedures\footnote{16} as well as for PVD imaging procedures\footnote{17} have been established and, though limited, such guidelines for intervention in PAD may be a first step in helping unify treatment of patients with vascular disease.

Disclosures
The authors have no conflict of interest relevant to this Editorial. Dr Shishehbor is an educator and consultant to Abbott Vascular, Medtronic, Cordis, Covidien, Spectranetics, CSI, Bayer, and Cook, but has waived all personal compensation for this work in the past 3 years.

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