ACHILLES and the Achilles Heel of Peripheral Vascular Intervention*

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In contrast to coronary artery disease in which a robust collection of data has demonstrated the merits of percutaneous revascularization, research investigating peripheral vascular intervention (PVI) has not yet matured in terms of magnitude, quality, or clarity. For example, only 1 randomized trial has assessed the efficacy of PVI relative to surgical bypass in patients with critical limb ischemia (CLI). That study was published more than 1 decade ago, and it examined what is now considered to be a rudimentary endovascular technique (e.g., balloon angioplasty [PTA]) (1).

Many technologies such as drug-coated balloons, drug-eluting stents (DES), and atherectomy devices have been developed in recent years to treat peripheral artery disease (PAD). However, randomized trials comparing the performance of these novel innovations against each other are largely lacking, and the PVI published data has become inundated with small observational data sets of suboptimal scientific value. Moreover, procedural success rates for PVI are exceptional, even in the most complex lesion subsets, but technical success and even long-term vessel patency do not always translate into meaningful clinical benefits for patients (2). As such, the lingering dilemma for clinicians performing PVI is no longer “can I open this artery?” but rather “how should I treat this artery and how will I define success?” Answers to the latter, the Achilles heel of PVI, remain unclear.

Within this framework, in this issue of JACC: Cardiovascular Interventions Katsanos et al. (3) report the 1-year wound healing and quality-of-life outcomes from the ACHILLES (Comparison of angioplasty and DES in the treatment of subjects With ischemic infrapopliteal arterial disease) trial. ACHILLES was a randomized study of 200 patients comparing balloon-expandable sirolimus-eluting stents (SES) with PTA for patients with infrapopliteal PAD. The primary analysis was previously published and demonstrated that SES use resulted in lower restenosis rates and improved vessel patency at 1 year (2).

In the present ACHILLES analysis, wound healing was assessed in 78 patients with 109 wounds, with roughly equal numbers of patients receiving SES and PTA (3). No differences were present in rates of wound closure or absolute wound reduction between the SES and PTA arms. The percentage of wound volume reduction was significantly better at 6 months in the SES group (95% vs. 60% volume reduction, p = 0.048), but this difference was no longer significant at 1 year due to “catch up” in the PTA group.

Health-related quality-of-life (HRQOL) was assessed in the entire ACHILLES cohort and wound subgroup using a validated questionnaire. HRQOL metrics improved in both SES and PTA groups at 1 year, but the change was statistically significant in only the SES arm. There was a trend toward more gain in quality-adjusted life-years in the SES group as well. Similar findings were present in the wound subgroup.

This ACHILLES analysis undoubtedly represents some progress for PVI research. Other randomized studies have investigated DES use in the infrapopliteal circulation. In general, these trials demonstrated improvements in patency and various clinical endpoints with DES use, but none have specifically examined wound healing or patient-reported HRQOL metrics (4,5). The authors are to be commended for providing data from a randomized PAD trial.
that examines whether drug-elution technologies can affect these important endpoints. Such findings are novel and represent a unique inclusion of patient-centric outcomes with traditional PAD trial endpoints such as restenosis, patency, and target vessel revascularization. On the basis of the finding of greater wound volume reduction in the SES arm at 6 months, the authors suggest that SES may accelerate wound healing. This assertion, if true, is particularly relevant because delayed wound healing may increase infection risk, adversely affect quality of life, and increase health care costs (6–8).

Despite these attributes, the principal findings of this analysis do have some limitations. Despite better patency and restenosis rates, the use of SES for infrapopliteal disease did not improve wound closure rates or wound healing at 1 year. If SES accelerate wound healing as the authors suggest, it remains unclear why similar rates of amputation and target vessel revascularization were noted. Moreover, although the improvement in HRQOL was significant only in the SES group, the baseline score in the PTA arm was objectively much higher, and this may have minimized the ability to identify a similar, statistically significant improvement in the PTA arm. Indeed, the 12-month HRQOL scores appeared qualitatively similar between the SES and PTA groups, and there was no incremental improvement in quality-adjusted life-years using SES compared with PTA. It is also difficult to ascertain whether the statistically significant changes in HRQOL reported represent any clinical impact because significant p values in HRQOL studies may not always correlate with patient benefit. Finally, mean lesion lengths were 2.6 cm and 3.2 cm in the SES and PTA groups, respectively. Most tibial disease encountered in clinical practice, particularly that in a critical limb population, is long, calcified, and multivessel in nature. As such, the widespread adoption of DES with existing technologies for tibial disease may be impractical.

In addition, the achievement of wound closure in patients with CLI relies on much more than establishing in-line flow to the foot. Emerging data suggest that limb salvage and wound healing rates may be better when using an angiosome-based revascularization strategy, whereby the tibial artery supplying the area of tissue loss is treated to restore direct perfusion (9). Medical treatment is also extremely important; for example, statin use before revascularization has been shown to be associated with improved limb salvage rates (10). Aggressive wound care, as part of a coordinated limb preservation program, can also impact wound healing. The current ACHILLES trial analysis did not account for angiogenesis-guided revascularization, and details on medication and wound care algorithms are not available.

In light of these considerations, what constitutes success with lower extremity revascularization? This is a complicated question that involves examining endpoints relevant to both clinicians and patients. Trials must include homogeneous populations when possible, as the treatment endpoints for claudicants may be far different from those with CLI (11). Additionally, standardized endpoints and definitions must be used so that accurate inferences can be made across different studies. Validation of patient-reported outcome measures will be needed to understand the magnitude of impact that a novel technology offers. Finally, sophisticated cost analyses will be needed to determine how to optimize treatment value for patients with PAD. With these refinements incorporated into a future prospective trial design and with the maturation of existing registries, many lingering questions will start to have answers, and many patients with PAD will begin reaping the benefits.

In the end, although the ACHILLES trial has demonstrated benefits in terms of restenosis and patency with SES use in infrapopliteal arteries, it remains unclear whether this translates into meaningful clinical benefit for patients. PVI research is moving in the right direction by beginning to focus on the right questions, but there is obviously much more to be learned.

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KEY WORDS angioplasty, critical limb ischemia, drug-eluting stent, peripheral artery disease, restenosis