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EDITORIAL COMMENT

Peripheral Artery Disease Therapies May Perform Differently in Practice Than in Randomized Trials

The Need for Learning Health Systems*

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The treatment of symptomatic femoropopliteal occlusive disease is a frequently encountered clinical problem for peripheral interventional operators. As the landscape for peripheral vascular intervention (PVI) continues to evolve, new therapies for patients with femoropopliteal occlusive disease, if proven durable and safe, would have widespread clinical appeal. Given the high incidence of peripheral artery disease (PAD) and the increasing frequency of PVI (1,2), a literature review surprisingly reveals very few studies being performed on patients with PAD. Specifically, an Agency for Healthcare Research and Quality report concluded that few published, comparative effectiveness studies in patients with PAD exist in the literature, and a review of the ongoing clinical studies involving patients with PAD (registered on ClinicalTrials.gov) represented only a small fraction of all studies on cardiovascular disease (3,4). This poses significant challenges to comparing new therapies with standard of care, but despite the underrepresentation of vascular patients in contemporary studies, new peripheral devices continue to be introduced into clinical practice in the United States, including reported breakthrough technologies like drug-coated balloons (DCBs). Although many of these pivotal studies of DCBs have a small sample size and lesion characteristics that fit very narrow inclusion criteria, the availability of DCBs for use in the treatment of all femoropopliteal occlusive disease has been met with great enthusiasm and optimism.

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In this issue of *JACC: Cardiovascular Interventions*, Schmidt et al. (5) report their single-center findings of 260 patients with femoropopliteal occlusive disease who underwent de novo peripheral vascular intervention (PVI) or reintervention for in-stent restenosis with paclitaxel-coated balloons (In.Pact Pacific or In.Pact Admiral DCB, Medtronic, Minneapolis, Minnesota). The patient demographic characteristics were similar to the cohort of patients randomized in the In.Pact SFA pivotal study (6); however, the patients included in the current study were more likely to have critical limb ischemia (CLI) and have a lower mean ankle brachial index. Given that restenosis was an exclusion criterion in the In.Pact SFA study, another major difference was that almost one-half of the patients included in the current study were treated for in-stent restenosis (37.2%) or restenosis with no previous stent (11.1%). From an angiographic perspective, the mean lesion length (24.0 ± 10.2 cm) in the current study was nearly 3-fold longer than that in the pivotal study, the proportion of chronic total occlusions treated (65.3%) was 2.5-fold greater, and the percentage of provisional stenting (23.3%) was 2-fold greater. By all counts, the current report represents a post-approval "real-world" clinical experience for DCB in patients with complex femoropopliteal occlusive disease.

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When reviewing the current results, the rate of periprocedural complications was high (2 distal embolizations, 1 acute stent thrombosis, 2 perforations) and likely reflects a more complex patient population, more complex target lesions, and use of adjunctive devices such as atherectomy and re-entry devices. The rates of all-cause mortality, clinical improvement (by Rutherford classification), and hemodynamic improvement (by ankle brachial index) were all consistent with previous literature on DCB and should likely be the focus of most reports. An inability to determine patency rates (26.0% at 2 years) and target lesion revascularization (TLR) (19.1% at 2 years) was a major limitation of the current study, and estimates of patency rates and freedom from TLR from the remaining cohort at 2 years were disappointingly low.

Although these findings represent an important contribution to the literature on PVI and the use of DCB, this study highlights multiple suboptimal aspects of evidence generation and suggests that PAD devices may perform differently in real-world practice when compared with randomized, controlled trials. First, the lack of an adequate contemporary comparator group limits all evidence generation and makes it difficult to determine how DCB technology compares with regular balloon angioplasty in routine clinical practice. Not only is it difficult to understand comparative safety and effectiveness, but the relative costs of DCBs (at least in the United States) are 3- to 4-fold higher than standard peripheral angioplasty balloons, a fact that is magnified given the use of multiple DCBs per patient in the current study. Second, patency rates and TLR were unable to be determined in 26.0% and 19.1% of patients, respectively; findings that were compatible with those of the In.Pact SFA study. This degree of patients lost to follow-up makes it difficult to interpret the 2-year findings as merely a "catch-up phenomenon" (a device-centric issue) or a significant limitation of clinical trials and clinical observational studies in PAD patients. Finally, with the complex nature of these PVI procedures and the collection of multiple data points such as the use of recanalization devices, atherectomy devices, provisional stents, and so on, the effectiveness and safety of a single device (DCB) used during an index procedure cannot be clearly delineated from the other factors without real-time large observational data sources.

In fact, it is this infrastructure and clinical understanding that will inform the future of clinical trials in patients with PAD. This begins with standard definitions and endpoints that can be applied across the clinical PAD space and include both patients with intermittent claudication and CLI. Examples of these include the consistent collection of functional and quality-of-life measures for patients with intermittent claudication and Wound, Ischemia, and Foot Infection scores for patients with CLI at multiple time points during the course of study (7). The Society of Vascular Surgery (SVS), American College of Cardiology/American Heart Association Task Force, and groups such as the Peripheral Academic Research Consortium and the Trans-Atlantic Inter-Society Consensus have published documents containing standard definitions and recommendations for use of these definitions in clinical trials and observational studies (8–11). Although this movement to incorporate standard definitions and measure clinical endpoints into routine practice has been termed a "learning health system," it is currently occurring in isolation at various hospitals and health systems in the United States. We suspect that it has not been occurring uniformly in the Unites States, especially since the available clinical registries (e.g., American College of Cardiology-Peripheral Vascular Intervention [ACC-PVI], Society of Vascular Surgery Vascular Quality Initiative [SVS VQI]) have a difference in nomenclature and capture data from operators based specifically on the operator's specialty (e.g., cardiology, surgery, radiology). Moreover, there has not been a strong clinical urgency to get real-time patient-level and system-level outcome data to improve clinical practice. This is changing with renewed pressures to demonstrate value and appropriateness.

Currently in the United States, 2 joint private-public partnerships with the U.S. Food and Drug Administration (FDA) called the FDA Sentinel Initiative and the Registry Assessment for Peripheral Interventional Devices (RAPID) have been formed to address these challenges. The FDA Sentinel Initiative was designed with the intent to understand safety issues using administrative claims data from the Centers for Medicare and Medicaid Services and large private health insurance companies. The RAPID project, a subset of the MDEpiNet program, was designed to create a common data model for PVI procedures, map data elements to electronic health records and current national registries (e.g., ACC-PVI, SVS VQI), and perform a randomized clinical trial using this infrastructure and background work. These public-private partnership efforts and the Best Endovascular vs. BEST-CLI (Best Surgical Therapy in Patients With Critical Limb Ischemia) trial (funded by the National Heart, Lung, and Blood Institute and endorsed by the FDA and multiple societies) also have the potential to include all PVI operators (i.e., surgeons, radiologists, cardiologists), academic and private hospitals, and

office-based clinics and the entire spectrum of current and future peripheral devices. Finally, it would open opportunities to more easily perform comparative effectiveness studies investigating treatment strategies such as atherectomy + DCB versus stenting.

However, these national initiatives will not have full effect until there are local, hospital-, or health system–level calls for real-time actionable reports on patients undergoing PVI. When combined with national programs, these programs have the potential to transform clinical trial methodology and significantly improve the performance of comparative effectiveness studies so that evidence generation will be easier, less costly, and more generalizable for patients with PAD. However, until the infrastructure is put into place so that we all use the same nomenclature and measure the endpoints that are important to patients, we will continue to be limited in our ability to make sustainable progress in improving the care of patients with PAD. The first step for the endovascular and surgical community of peripheral vascular clinicians is to embrace standardized clinical care and procedural notes that used structured data elements that can be harvested from the Electronic Health Record. Until then, all patients and clinicians will continue to struggle with the fact that peripheral artery devices may perform differently than reported in clinical studies.

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