The Future of Femoropopliteal Studies

A discussion on the challenges of applying current trial data and improvements that could guide evidence-based decision making.

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We have finally seen long-term (3–5 years) primary patency data from randomized trials of drug-eluting stents (DESs), drug-coated balloons (DCBs), and wire interwoven stents.[1,2] We now have many options to treat the femoropopliteal segment, including combination therapies such as atherectomy with DCB.[3] Newer devices are continuously being developed or are under investigation, such as second-generation DCBs, extravascular percutaneous bypass, ultrasound-based balloons, and other adjunctive therapies. However, despite these advances, the femoropopliteal segment continues to be a challenge in the real-world setting.[4]

CHALLENGES OF CURRENT TRIALS

Lack of Real-World Patients

One challenge regarding current trial data is the disconnect between the patients who are typically considered for trials aimed at gaining regulatory approvals and the real-world experience. The majority of patients enrolled in these trials have short lesions (mean lesion length, 7–8 cm) with stenotic rather than occlusive disease that contains mild to moderate calcification. Importantly, high-risk segments (common femoral artery, ostial superficial femoral artery [SFA], and popliteal artery) and poor runoff are frequently not included. Furthermore, almost invariably, patients with Rutherford class 5 and 6 disease—the individuals with worse disease—are typically excluded. Therefore, the true patency of these devices in long lesions is not well defined.

Most recent postmarket registries have allowed a better understanding of the efficacy and safety of these technologies in a real-world setting; however, many of these registries are voluntary and do not include core lab adjudication.[5] They rely heavily on soft endpoints, such as target vessel revascularization versus ultrasound-based patency or clinically driven target vessel revascularization, and lack data on quality of life metrics. In the future, well-conducted mandatory national postmarket registries with core lab adjudication should be required so that important reliable information regarding patency and safety for various devices in real-world patients can be obtained. This effort has already been successful in patients undergoing transcatheter aortic valve replacement.

Need for Next-Generation Randomized Controlled Trials and Postmarket Registries

Another important need is a head-to-head randomized controlled trial (RCT). We currently have an armamentarium of devices, including atherectomy, percutaneous transluminal angioplasty (PTA), nitinol stents, DESs, DCBs, wire interwoven stents, covered stents, and combination therapy to treat the SFA.[3] However, to date, comparative data primarily only exist against PTA or previous-generation bare-metal stents. Although RCTs that compare the various treatments may not be cost-effective or realistic, well-conducted, multicenter, postmarket registries that capture similar baseline and procedural characteristics and require core lab adjudication are badly needed. This is the only way physicians can truly make evidence-based decisions when treating patients with femoropopliteal disease. Additionally, despite the challenges, industry partners should be encouraged to continue to pursue these head-to-head trials. The recently announced head-to-head trial comparing the Chocolate DCB (QT Vascular) versus the Lutonix DCB (Bard Peripheral Vascular, Inc.) is a step forward in this direction.

Postmarket registries appear to provide additional efficacy and safety data beyond investigational device exemption RCTs; however, they too have many limitations. Beyond those mentioned previously, one of the

challenges of these registries is their availability for public viewing and analysis. Many, if not all, are managed and owned by respective industry organizations; therefore, the validity and output from these registries may not be free from bias. Furthermore, comparative analysis and data sharing are rarely performed; hence, they never reach their potential and are frequently used for marketing purposes alone. The ideal postmarket registry should require that all cases be captured (to prevent selection bias) and available to scientists and the public for careful analysis and publication independent of industry.

As mentioned previously, all trials evaluating femoropopliteal disease have excluded patients with Rutherford class 5 and 6 disease, which is another important limitation of current devices for the femoropopliteal segment. Although many devices should be safe for patients in any Rutherford class, the safety of some devices such as DCBs or DESs in patients with ulcers and gangrene is not well known.[3] Moreover, although patency and clinically driven target vessel revascularization are considered important primary endpoints in those with claudication, they may not necessarily be sufficient for patients with critical limb ischemia.[6] We desperately need data regarding the safety of these devices in patients with tissue loss and in those with poor runoff. However, the data derived from postmarket registries are also limited in their inclusion of patients that match real-world scenarios.

Evaluating Costs Versus Relevant Endpoints

The Affordable Care Act has also changed the landscape of care for patients with femoropopliteal disease. The challenging question we must answer is: what are the most cost-effective therapies for patients with femoropopliteal disease? Unfortunately, the current cost-effectiveness data are limited to comparative data against PTA.[7] Although valuable, these data provide little help to physicians in selecting the most cost-effective device for treating patients with SFA disease. It is unlikely these data will be obtained from an RCT, but well-conducted comparative postmarket registries should help provide this important information.

The issues related to comparative effectiveness will likely become even more relevant in the next few years with the current move toward bundle payments and public reporting. Because of these changes, institutions, payers, physicians, and patients are all interested in the most effective, cost-conscious, and safe technology.[8] Without level 1 data or excellent high-quality postmarket registries, these decisions may be made completely based on cost. This is already happening with cost repositioning and the creation of purchasing committees and device consolidation in many institutions.[8] Without a clear benefit, more advanced and costly devices are less likely to be purchased or available for use in most institutions.

Quality of life, improvement in pain, fast healing, and reduced readmissions are other important endpoints that must be considered so that important therapies continue to be available for patients with peripheral artery disease. This is extremely important given the Centers for Medicare & Medicaid Services' goal to reduce cost. In a recent Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) review and analysis, many MEDCAC panel members found that endovascular or surgical revascularization is not very effective in treating patients with claudication despite overwhelming support by a coalition of seven societies and organizations.[9] It is therefore critical that future trials that evaluate devices for the SFA and popliteal artery clearly demonstrate not only better patency but also improvement in other important endpoints, such as quality of life, pain-free walking, time to wound healing, time to ambulation, and reduced hospital readmissions and office visits.

There have been many advances in telemedicine and wireless technologies. It is conceivable that by using smart devices, we could reduce the cost and burden of RCTs so that more comparative effectiveness trials can be conducted. For example, many smart devices can now measure steps, speed, and other important endpoints. Using such technologies would also allow continuous monitoring of these important endpoints without the need for frequent follow-up and office visits, which is one of the main reasons patients do not participate in these trials.

Subjective Device Sizing

Another important aspect of an RCT for the femoropopliteal artery is appropriate sizing of devices. We continue to treat the femoropopliteal artery with devices that are subjectively sized, which has been shown to lead to an increase in restenosis in multiple studies.[10-12] A future RCT of devices for the SFA and popliteal artery should incorporate image-guided intervention to achieve the best results.[13] Furthermore, we need trials and data to support adjunctive imaging to help guide SFA and popliteal interventions. Unfortunately, at the present time, intravascular ultrasound, fractional flow reserve, or optical coherence tomography are not reimbursed in the United States for use in the lower extremities.

Lack of Granular Data

A series of national registries are currently available, including the Society of Vascular Surgery Vascular Quality Initiative and the American College of Cardiology Peripheral Vascular Intervention National Cardiovascular Data Registry. Although these registries will be informa-

tive and will help us understand best practices, they are unlikely to provide enough granular data for comparative effectiveness among various devices. The main reasons for this are inadequate follow-up, lack of standard endpoints, and significant emphasis on institutionally available data. Is it possible that an RCT can collaborate in parallel with these large national registries so that more real-world data can be collected, but importantly also reduce cost while providing enough granular data so that comparative analysis between devices can be made?

FUTURE DIRECTIONS

In the next 5 to 10 years, we must begin to treat the femoropopliteal artery not as one unit but rather as segments, the so-called segmental approach. A device that may be very effective for the proximal and mid SFA may not function well in the distal SFA and popliteal artery because of flexion, elongation, torsion, and motion. Similarly, some devices may work well in moderate to severe calcifications, while others may be effective in soft nonocclusive plaques. Decisions regarding the best device for the SFA and popliteal artery should be based on location, plaque morphology, calcification, type of disease (stenotic vs occlusive), length, and underlying disease (claudication vs critical limb ischemia). Future trials may need to incorporate multiple devices that are appropriate for each segment for best outcome. This will only occur if the regulatory bodies remain dynamic and we as physicians continue to demand it. ■

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