ASK THE EXPERTS

How Can Current Endpoints in Below-the-Knee Clinical Trials Be Improved?

Experts discuss how to better align trial endpoints for improved assessment of below-the-knee outcomes in patients with critical limb ischemia.

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Trials investigating new treatment modalities for femoropopliteal artery disease are designed to evaluate two major primary endpoints. The first is technical success, which is longer-term patency or late lumen loss for revascularization trials to prove efficacy of the test modality. This technical endpoint is supplemented by a coprimary endpoint that evaluates safety, most often a composite endpoint of event-free survival, and a series of secondary clinical endpoints.

However, endpoints of trials that include claudicants with femoropopliteal artery disease can be analyzed objectively (eg, restenosis rate as a technical endpoint assessed by duplex ultrasound, pain-free walking distance assessed by treadmill test, and quality of life [QOL] assessed by questionnaire). Symptom relief is strongly correlated to target vessel patency and rarely depends on cofactors. However, the conditions for below-the-knee (BTK) trials are much more challenging.

First, objective determination of technical endpoints can only be done using angiography. This results in high dropout rates due to death, concomitant diseases, and unwillingness to participate in follow-up angiography. Second, the main indication for tibial artery revascularization is limb preservation and pain relief. As such, most BTK trials include patients with critical limb ischemia (CLI) or what I regard as "pseudo-CLI" (eg, patients with diabetic foot syndrome and accompanying peripheral artery disease that does not meet the true definition of CLI as defined by the Rutherford-

Becker criteria). The inclusion of a high proportion of patients with diabetes mellitus in CLI trials adds important covariables other than target vessel patency, affecting the outcome of the most relevant clinical endpoints (eg, rest pain can be attributed to diabetic neuropathy, wound healing speed depends on the quality of glycemic control as well as the stage of wound infection and infection control). Moreover, the quality of wound care differs from patient to patient and center to center and adds another variable. As a result, the correlation of technical efficacy of tibial artery revascularization and clinical improvement is not as close as in a claudicant population, resulting in significant bias by multiple cofactors that can hardly be standardized.

As a result, angiographic endpoint–driven pilot studies should be performed as a first step of a clinical BTK trial program to prove efficacy in a well-defined patient cohort without significant comorbidities to ensure a low loss of follow-up. Next, inclusion criteria for BTK trials driven by clinical endpoints should be reconsidered, either to exclude patients with diabetes mellitus or, in the case of randomized trials, running two independent randomization protocols for patients with and without diabetes mellitus. Otherwise, trials would need to include thousands of patients to prove the concept of tibial artery revascularization for limb preservation.

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I think certain general concepts should be considered when designing studies or evaluating the results of a trial in patients with CLI. The objectives of therapy in these patients should and do revolve around life, limb, pain, and function. However, much like cancer research, we could entirely miss the beneficial effect of a therapy if we do not measure the right parameters. As far as evaluation of new techniques, devices, and treatment strategies are concerned, we need to keep the many parallels between cancer and CLI patients in mind.

- Progress in both fields is often incremental, and giant leaps are rare. Preservation of life or limb often requires instituting many therapeutic steps (eg, pain and infection control, management of risk factors, optimal wound care, revascularization) and is affected by many variables. Testing the impact of only one step in the therapeutic chain may not demonstrate an overall treatment effect on limb salvage or survival. For example, restoration of blood flow, while necessary, is not the only factor determining limb salvage. Hence, technologies that improve the extent and duration of blood flow may be overlooked or dismissed if limb salvage was the only outcome evaluated. Every therapy adding incremental improvement should be tested on its own merit with endpoints sensitive to what the therapy is designed to achieve (ie, improve patency, reduce thrombosis, minimize reintervention rates, prevent infection).
- Given the incremental nature of progress in CLI research, most practitioners agree that there is a paucity of diagnostic tools to accurately measure potentially important parameters such as blood flow, tissue oxygenation, perfusion or metabolism, and rate of wound healing. Sensitive methods to assess a therapeutic effect should be developed and validated in this patient population.
- Due to the diversity of the population in general and CLI patients in particular, a new therapy may not show a positive treatment effect in everyone. There are genetic, physiologic, and anatomic variations that may predispose one group to a better or worse outcome than others. Particular attention has to be made to subgroup analyses and secondary endpoints, which can be important learning tools to guide future treatments and follow-up trials.
- Life expectancy of CLI patients should be considered when designing therapeutic tools and trials to test them. Approaches that improve the QOL for even a short duration are often significant to this patient population. Hence, short trial durations such as 6 months are entirely appropriate in CLI trials. Longer follow-up is of course desirable, but a "catch-up" phenomenon, while important to investigate, should not discount the value of a new treatment when present. Cost-effectiveness of therapies with either short or small impact will ultimately drive utilization and market adoption. Manufacturers should be sensitive to such when pricing their technology.

- Safety and avoidance of pain and suffering should be as important as durability of a therapeutic plan in this patient population. Measures to evaluate QOL or pain and suffering are relevant endpoints.

Considering the aforementioned points, here are my thoughts and recommendations:

- Trials often set the standard of care, and hence, all aspects of therapy should be optimized and standardized, even if only a single step is the focus of the investigation.
- Endpoints have to match what the new therapy is designed to do. We need to ask if we are measuring the right variables in the right patients before executing a trial.
- To identify the treatment effect of a new therapy, extremes of disease severity should be avoided (too sick or too healthy).
- Due to the poor QOL and short life expectancy of patients with CLI, frequent follow-up and short times to endpoint assessments are appropriate and necessary.

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Discussions around endpoints are complex, and it is worth considering what each brings to the table. BTK trials have traditionally used endpoints that fall into five categories:

1. Technical success (device/procedural success and freedom from procedural complications) and safety (major adverse events and death)
2. Evaluation of restenosis (binary restenosis > 50%, late lumen loss)
3. Reintervention rates (target lesion revascularization [TLR] and target vessel revascularization, usually defined as clinically driven [CD])
4. Clinical outcomes (Rutherford category; wound healing rates measured by complete healing, area, depth or volume reduction; minor/major amputation rates and limb salvage)
5. Composite endpoints

Commonly used composite endpoints include but are not limited to primary patency (freedom from target vessel occlusion, CD-TLR, or binary restenosis), amputation-free survival (freedom from major amputation or death), and combined safety endpoints (all-cause death, major amputation, or CD-TLR). This is where endpoints get complicated, and there is often inconsistency between BTK studies and the vascular surgical literature. Moreover, these combined endpoints may overlap to include multiples of the same index endpoint within the newly defined matrix.

In my view, we have too many endpoints and many that are inherited from coronary trials, which are less relevant to BTK. We also focus our attention on patency when this outcome may be less relevant to CLI. Endpoints should be reduced to those that have significant value, address the clinical question at hand, and have precise, consistent definitions.

BTK trials should keep the endpoints simple, explicit, objectively defined, and matched to the research question. If a trial aims to evaluate a device for the first time, it should use endpoints that measure safety and device success. If a trial's objective is to assess an intervention that is thought to have improved antirestenotic properties over the standard of care, then it should use measures of restenosis (late lumen loss and binary restenosis). If the research question is related to clinical utility of a product or device, then it should use clinically relevant endpoints, such as change in Rutherford category, CD-TLR, wound healing, and major amputation and limb salvage rates.

There is certainly a place for composite endpoints, which can be grouped into similar themed but low-incidence outcomes to demonstrate a benefit of one treatment over another. However, to add value, they must be objectively defined and consistent between studies to facilitate comparison. I believe there is a place for the development of reporting standards and objective performance criteria by endovascular specialists, akin to those in the vascular surgical literature.[1,2] These would facilitate a clear understanding of the endovascular literature and validate treatment comparisons for those that read and conduct clinical studies in BTK disease.

1. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997;26:517–538.
2. Conte MS, Geraghty PJ, Bradbury AW, et al. Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. J Vasc Surg. 2009;50:1462–1473.

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We use the same endpoints in BTK trials as we use in above-the-knee trials to prove the efficacy of new devices, namely primary patency and CD-TLR. For CLI, we add limb salvage as an endpoint. The main issue is that we mix the proof of concept of a new treatment modality in a dedicated arterial bed with the most severe form of peripheral artery disease.

It is not relevant to only evaluate patency of a treated vessel segment to assess outcomes for limb salvage. The endpoint of limb salvage is influenced by many more factors, such as wound infection and wound care. We evaluate the above-mentioned endpoints for CLI patients on the same timelines as we evaluate those endpoints for claudicants who present with a much less severe form of peripheral artery disease. For the timelines we use now, we have poor results for vessel patency because disease is so progressive in the BTK vascular bed, especially in combination with CLI. We do not have the adequate hemodynamic parameters (ie, adequate mapping) to guide us through our BTK interventions.

How do we improve these endpoints? To establish the proof of concept of a new treatment modality, it should be proven in the context of the same disease (ie, above the knee or BTK). For better outcomes in CLI patients, we should look to incorporate new "mapping/guidance" technologies into our interventions to allow us to reopen the adequate pathway down to the relevant tissue loss area. ■