PANEL DISCUSSION

Surveying the Below-the-Knee Revascularization Trial Landscape

Trialists discuss lessons learned from key CLI/CLTI trials, including BEST-CLI, BASIL-2, LIFE-BTK, and SAVAL.

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The past few years have seen the emergence of a long-awaited new generation of randomized data for critical limb ischemia/chronic limb-threatening ischemia (CLI/CLTI), with several key trials presenting and publishing their findings in this timeframe. These include BEST-CLI, BASIL-2, LIFE-BTK, SAVAL, and others. At times confirmatory of one another and others disparate, the field has had much to pore over in each data set.

Did the BEST-CLI results affect your practice algorithm? If so, were there further changes after BASIL-2?

Dr. DeRubertis: BEST-CLI should significantly impact the practice of many surgeon and nonsurgeon interventionalists, considering how dominant a role endovascular therapy has become for treating patients with CLTI. Although percutaneous techniques have been extremely useful for many—even a majority—of these patients, it was nevertheless shown in BEST-CLI that there is a subset of patients who benefit more from surgical bypass than endovascular intervention, and this is true over a number of metrics. However, it needs to be remembered that the patients treated in BEST-CLI represented a very selected patient population that was screened, and this is a small portion of all patients treated within each of the study sites for CLTI.

So, the key in applying these results is identifying which of our patients are similar to those randomized in BEST-CLI, because I think it is overly simplistic to say that all patients with adequate great saphenous vein (GSV) should be treated with bypass. On the other hand, BEST-CLI showed something that, as surgeons, we always knew to be true. There are some patients who require such an increase in perfusion above baseline—and one that needs to be sustained for many months to allow for wound healing—that bypass surgery is the obvious choice. This includes patients with extensive multilevel disease with large-volume tissue defects that will take long periods of time to heal their wounds. I do think that many skilled interventionalists confuse the technical ability to perform complex percutaneous revascularizations with the notion that endovascular therapy is the right choice for all patients. BEST-CLI disavowed us of this idea.

BASIL-2 was a very important addition to the space and this question, in part because it mandated that patients had infrapopliteal disease in order to be randomized. The conflicting results with BEST-CLI may in part be due to this additional inclusion requirement, and it highlights the fact that our surgical therapy may not always address the most distal tibiopedal-level disease, and that endovascular therapy may have some additional advantages here.

This last point is why trials like SAVAL and LIFE-BTK are critical to the space. These trials are not focused on the overall treatment strategy (like BEST-CLI and BASIL-2) but instead target device approval, and specifically approval of devices for the below-the-knee (BTK) space, which BASIL-2 suggests is critical to optimal outcomes.

Dr. Farber: Yes, BEST-CLI has affected our clinical algorithm to treat patients with CLTI at Boston Medical Center. Now, we always obtain saphenous vein mapping before we perform angiography in patients with CLTI who are candidates for surgery to determine whether saphenous vein bypass might be an option. BASIL-2 has not significantly changed my outlook except to remind me that patients with CLTI have an incredibly high mortality and that we really need to focus on how to mitigate that.

Dr. Geraghty: Both the BEST-CLI and BASIL-2 results were largely congruent with my current practice for CLTI patients. In addition to arterial noninvasive testing, we routinely map the saphenous conduit and frequently perform aortoiliofemoral CTA for procedural planning. Patients with adequate GSV are offered bypass, particularly if they have common femoral artery/ostial superficial femoral artery involvement and contiguous multilevel disease. We engage in shared decision-making, and some patients will elect to pursue endovascular therapy despite the BEST-CLI findings. In addition, a substantial (and growing) number of my CLTI patients have advanced infrapopliteal calcific disease associated with longstanding diabetes and/or end-stage renal disease (ESRD). These patients are rarely good bypass candidates due to extensive vessel calcification, and our default approach in that setting has been endovascular treatment, which mapped well to the BASIL-2 trial results.

Prof. Saratzis: The population of patients included in BEST-CLI is very heterogeneous in terms of anatomy, and I can't really say that this study has completely changed my practice or our unit's approach to offering bypasses versus endovascular treatments. It has reinforced the message that bypass is a safe and durable procedure in those patients who are fit enough to undergo open surgery, preferably with a venous conduit. With regard to BTK disease, BASIL-2 has definitely influenced our practice, with endovascular approaches preferred as a first option for those who present with crural disease.

If your approach has not changed, what findings would have a larger impact?

Prof. Saratzis: We are all looking forward to the combined patient-level meta-analysis as well as the full BASIL-3 manuscript with all relevant results. These study data together should inform practice regarding the most clinically

and cost-effective approach per anatomic segment in the infrainguinal region (femoropopliteal vs crural).

Dr. DeRubertis: I believe these trials haven't necessarily changed practices in a dramatic way as much as they have highlighted the fact that decisions between open surgery and endovascular therapy have to be individualized to the patient and clinical circumstances. It also seems that the complex and nuanced interpretation of these trials will ultimately lead us to the conclusion that we should not be putting these two options in opposition but rather recognize that they are complementary and should be used as two equally valid components of our CLTI arsenal. Although further subset analyses (ie, comparing the patient populations in BEST-CLI and BASIL-2) can further help us understand some of these nuances, I don't honestly believe any more findings or data in this area will change this fundamental fact.

How do you reconcile the different results in these trials (eg, how BEST-CLI and BASIL-2 had some similarities but substantial differences)?

Dr. Farber: Professor Andrew Bradbury, the Principal Investigator of BASIL-2, is a close friend and provided input to Drs. Matthew Menard, Kenneth Rosenfield, and me in the planning of the BEST-CLI trial. Together, our groups sought to bring evidence base to the field. Comparing BEST-CLI and BASIL-2 is in some ways like comparing apples to oranges, and I can point out how these trials are different. To start, BEST-CLI was mostly conducted in North America, with a few sites in New Zealand, Finland, and Italy. BASIL-2 was conducted mostly in the United Kingdom with sites in Denmark and Sweden.

The trials were different in magnitude. In BASIL-2, trial leadership planned to enroll 600 patients but ended up enrolling 345 patients. In BEST-CLI, we enrolled 1,830 patients. Patient populations in these trials were very different. BASIL-2 had fewer women, fewer patients of color, and fewer patients with ESRD. Significantly more patients in BASIL-2 had a history of prior revascularization and more tibial disease because the trial focused on the infrapopliteal segments, whereas BEST-CLI looked at both infrapopliteal and suprapopliteal disease. There was also significantly less use of drug elution in BASIL-2 and much more use of balloon angioplasty alone.

The primary outcomes were also different. Our primary outcome was major adverse limb events (MALE) or all-cause death, whereas for BASIL-2 it was amputation-free survival (AFS). Technical failure in the endovascular arm was similar between the trials (14% in BASIL-2 and 15% in BEST-CLI cohort 1) even though the majority of endovascular cases were performed by interventional radiologists in BASIL-2, whereas vascular surgeons performed most endovascular cases in BEST-CLI. Perioperative or 30-day mortality was much higher in BASIL-2—6% for bypass versus 1.7% for BEST-CLI—that's a significant difference. At median follow-up, 53% of patients in BASIL-2 in the bypass arm died as compared with 33% in BEST-CLI. Amputation rates were also higher in BASIL 2 (20% vs 10%).

When you look at all of this information together, it appears that BASIL-2 is driven by long-term mortality. It is important to note that the original plan was to enroll 600 patients, but because the event rate was high and there were difficulties in recruiting exacerbated by the COVID-19 pandemic, BASIL-2 investigators decided to decrease the target number of patients. A consequence of this is that the study was less powered for limb events that usually occur early in follow-up.

I think that the differences that we're seeing are related to both patient and procedural factors. These differences may also be a consequence of the differences in the health care systems in the United Kingdom and North America. Therefore, more granular comparison is needed, and the teams of both studies are working on that. We plan to do a patient-level meta-analysis to see how to best harmonize and reconcile these findings.

Prof. Saratzis: In many ways, BEST-CLI was similar to the original BASIL trial. Patients predominantly had femoropopliteal disease, and the endovascular arm did not include a considerable proportion of newer endovascular technologies such as vessel preparation devices. It is therefore not surprising that bypass was superior. The combined meta-analysis will hopefully shed some light into this. Furthermore, it is important to note and consider the fact that the two trials have looked at two separate anatomic segments in different health care systems.

Dr. Geraghty: This wasn't an instance of identical trials yielding different results. Both were pragmatic trials but with significant differences in design—most notably, the anatomic distribution of disease (infrainguinal vs infrapopliteal) and the selected primary outcome measures (MALE plus all-cause death vs AFS plus all-cause death). Given the prominent differences in the design of the two trials, it was not surprising that we have seen variance in the outcomes.

Dr. DeRubertis: There are obviously many differences between these trials, including the requirement of infrapopliteal disease in BASIL-2, the total number randomized in each trial, the perioperative mortality in the surgical arms, and, perhaps most importantly, the primary endpoints. This last point is an important one, as postoperative mortality in BASIL-2 largely drove its endpoint, while

reintervention significantly drove the BEST-CLI endpoint. Both of these endpoints have been criticized for these reasons, as nonprocedural-related mortality is overly weighted in the former, but what are relatively nonimpactful reinterventions are overly weighted in the latter. Debate about the relative merits of each of these endpoints will continue indefinitely, as these endpoints certainly play some role in the discrepant outcomes.

What has the current class of trials told us about operator experience and outcomes?

Dr. DeRubertis: It is important to recognize the relationship between operator experience and patient outcome because, especially for a trial like BEST-CLI, there is likely a wide range in operator experience. This plays prominently in decisions regarding the concept of equipoise that is required for randomization. Additionally, the technical success rate in the endovascular arm for BEST-CLI impacts the endpoint, and many have commented on the fact that a roughly 15% failure rate is not what most of us see in our own practices. These considerations must be kept in mind when we evaluate the nuances of these trials.

Prof. Saratzis: BASIL-2 and BEST-CLI managed to recruit a rather small proportion of the patients treated in the institutions taking part, which is expected given the characteristics of people with CLTI and challenges regarding recruitment in such interventional randomized studies. This should be a wake-up call for all vascular clinicians. We can do better as a community of vascular experts and recruit far more efficiently in such randomized trials and across more institutions. This should hopefully address issues regarding interpretation of trial results in the context of operator and center experience and expertise. The trials as published cannot really be used to make any safe assumptions regarding operator experience or impact on outcomes.

Dr. Farber: These larger trials have been pragmatic and multispecialty. They demonstrated that good outcomes can be achieved by operators with both bypass and endovascular therapy. There's no question that both revascularization strategies have a role. We need to do more to figure out which strategy is best for which patient. BEST-CLI was a "real world" trial with interventions performed by multiple investigators. These investigators had good results with both types of interventions.

Dr. Geraghty: My take is unique but hear me out—I believe that the single-most important lesson from these trials is that our preconceptions regarding the outcomes of these interventions were frequently wrong. That's humbling, but if we recognize how fallible and self-serving our opinions can be, then we can truly appreciate the need to base our treatment choices on empirical evidence whenever possible. Unfortunately, there was a great deal of confirmation bias and flawed inductive reasoning on display after the BEST-CLI trial release. Much of it had to do with the technical failure rates for endovascular intervention. I suspect that lesion crossing rates have improved over time and that enhanced lesion crossing might translate into more favorable endovascular outcomes, but that's an opinion, not a fact. And my opinion—even if shared by many capable interventionalists—doesn't refute the study data. Fortunately, we have the option of generating an updated comparative data set that could prove our contention. At the end of the day, that's what our field needs: more data, more science, more humility, and less opinion.

Reflecting on the role medical management played, what were the key lessons learned regarding medical management in your trial? What has been learned in recent trials that can be implemented into today's practices?

Dr. Farber: This is a really important question. There are several published papers on this topic, including an article by Menard et al on baseline medical therapy,[1] as well as an upcoming paper with some exciting medical therapy data that I can't share just yet. What I can share with you is that BEST-CLI had an Optimal Medical Therapy (OMT) Committee led by Dr. Michael Jaff, which delineated guideline-directed medical therapy that investigators were encouraged to use on their patients. Dashboards of OMT use (antihypertensives, statins, and antiplatelets) were provided to investigators where site performance in OMT use was benchmarked across trial sites.

In our *New England Journal of Medicine* article, we reported baseline OMT and this led to misinterpretation. OMT use increased significantly at 30 days after revascularization. For instance, 75% of patients in cohort 1 at 30 days were on a statin. If you look at what's out there in the literature, it's within range of what's been previously published.

These trials have taught that vascular physicians need to be proactive about managing their patients using medical therapy and not assume that the primary care/family practice physician is managing it.

Dr. Geraghty: We have much room for improvement in achieving our OMT goals (eg, high-intensity statin). We need consensus on duration of postprocedural dual antiplatelet therapy (DAPT). Aspirin plus rivaroxaban regimen and PCSK9 inhibitors influence MALE rates and outcomes, so these factors must also be tracked and analyzed.

Prof. Saratzis: It is difficult to standardize medical management and lifestyle changes in people with CLTI in the context of a randomized study. At the same time, we have shown that medical treatment and exercise/risk-factor control are key constituents of peripheral artery disease (PAD) care, especially when intervening with surgery or endovascular procedures.[2] In EVOCC (an ongoing trial in PAD), we have adopted a pragmatic approach and left medical management to a local team to deal with while collecting data regarding medication and lifestyle during follow-up. We will be reporting subgroup analyses based on risk factors and medical management as well. Randomization should address most issues relating to medical care differences in well-designed efficacy-driven randomized controlled trials (RCTs), at least at baseline.

Dr. DeRubertis: This is an area that has yet to be fully mined for all the lessons that can be learned. Even when specific medical therapies are mandated in trials, there can be variability in adherence to these practices during the conduct of the trial. In the case of the LIFE-BTK trial, only the scaffold arm was required to undergo DAPT; yet in looking at the results, we found that both arms had similarly high rates of DAPT use. We are currently in the process of preparing a manuscript that explores the impact of medical therapy in these patients.

What has been learned from the outcomes in the various percutaneous transluminal angioplasty (PTA)/control arms from RCTs comparing PTA to scaffolding (LIFE-BTK and SAVAL, as well as IN.PACT DEEP and Lutonix BTK)? In the study arms, are there any new lessons learned regarding stent placement?

Prof. Saratzis: Such efficacy-driven RCTs are very difficult to extrapolate in everyday practice given the exclusion criteria used in most of these trials. Our recent work clearly showcases this—in the pan-European RANDOM-STOP study, we found that > 80% of PAD patients treated in 17 vascular centers would not have been eligible for inclusion in the seven major RCTs assessing paclitaxel-based treatments in femoropopliteal PAD.[3]

Dr. DeRubertis: Across many trials, we have seen the PTA arm come in with results that are unexpectedly favorable, and this demonstrates the impact of the technique, even with something as simple as balloon angioplasty. However, we ultimately need to design trials whose comparator arm is consistent with standard of care. For example, if the mandated PTA technique in an RCT requires several prolonged balloon inflations that are not what is done in clinical practice, this could skew the outcomes in ways that make an effective trial device appear less effective by comparison. Regarding stent or scaffold placement, the LIFE-BTK trial is the most relevant trial pertaining to this issue. In this trial, we carried over lessons from the ABSORB coronary trials and applied them to this trial to ensure that optimal technique was achieved for stent implantation, and we encouraged the use of intravascular ultrasound (IVUS) to aid with sizing and postimplantation assessment of scaffold apposition. There will undoubtedly be additional learnings that will come from subsequent analyses of these data.

Dr. Geraghty: Here are three nuggets from the investigational device exemption (IDE) trial data that bear consideration: First, unpublished data suggest that the sensitivity of duplex ultrasound is much poorer than control angiography in detecting arterial occlusion. Control angiography should therefore be a component of IDE trials. Second, even experienced interventionalists tend to underdilate the infrapopliteal arteries, with poor results. If you don't have IVUS for guidance, perhaps consider serially dilating to a vessel diameter 0.5 or 1 mm greater than your angiographic eyeball estimate. Finally, multiple inflations may improve outcomes in tibial angioplasty. Drug-coated balloon (DCB) IDE trial protocols called for predilation, followed by randomization and then index treatment with plain old balloon angioplasty (POBA) or DCB. The end result was that lesions received two nominal inflations, and the results for POBA exceeded expectation, with superb primary patency and extremely low rates of stent bailout. This finding deserves further investigation.

Demographically, what can you tell us about how representative your trial's population was and how it compares to the populations typically treated in the regions where patients were enrolled? What measures should be taken to ensure inclusion of underrepresented populations?

Dr. DeRubertis: For some time now, it has been recognized that our clinical trials do not necessarily include the diverse patient populations that we treat on a day-to-day basis. This likely has to do with a number of issues, including the fact that the resources involved in running clinical trials may not be equally available in all geographic and practice settings. This obviously impacts the generalizability of these trials' findings to the overall patient population we treat. For this reason, we sought to include these underrepresented patient populations in the LIFE-BTK trial, and to do so, we not only encouraged enrollment of diverse patient groups at each site but, more importantly, we specifically selected trial sites that treated geographies or patient groups not typically

included in randomized trials. I believe the purposeful inclusion of these practices to increase patient diversity will set the stage for other clinical trials to follow suit.

Dr. Geraghty: Within the IDE trials, physician investigators and their industry partners are always attentive to achieving appropriate demographic distributions, including underrepresented populations. However, these trials are frequently global in nature, and the variable population characteristics of the participating European Union and Asian nations ensure that the trial cohort will differ somewhat from the United States population.

Dr. Farber: RCTs are powerful because they decrease confounding and eliminate spurious causality. They're the gold standard of research; however, they're expensive and they take a long time to complete. In addition, questions of generalizability of trial findings to the broader population are often asked.

BEST-CLI did not include all patients with CLTI. Only those patients who were candidates for both open and endovascular strategy and who were at an acceptable risk for surgery were included. In cohort 1 (those with adequate single segment GSV), 80% of the patients had tissue loss, two-thirds had severe tibial disease, and 72% had diabetes. This is what one would expect to see in a population of patients with CLTI. We excluded patients at high risk for surgery, those who had straightforward arterial anatomy (TASC II A disease) and patients who had a history of prior endovascular interventions with failed stents.

There has been an interest to compare the BEST-CLI patient population to other so-called "real-world" cohorts. However, analysis of such studies does not allow for elimination of confounding. Many of these databases are biased because current practice is commonly to treat patients with endovascular intervention first and many endo patients are not amenable to surgery. In addition, many surgical patients have complex disease and have had prior interventions.

The most optimal comparator is a concurrent registry. Although this was not available, researchers from Duke did collect data from a nonconcurrent registry at 40 BEST-CLI sites. These data are currently being evaluated and will be published in time.

To get a sense of generalizability in our trial, we performed a "back of the envelope" comparison of BEST-CLI with the Vascular Quality Initiative (VQI) registry. Patients in BEST-CLI were younger, had less ESRD, has less congestive heart failure, and less chronic obstructive pulmonary disease than similar VQI patients. However, they had more coronary artery disease and diabetes. What does that mean? It's not clear. More work is needed in this space.

In BEST-CLI, almost 30% of patients were people of color. The National Heart, Lung and Blood Institute set goals for us for inclusion that we superseded, which we are very proud of. Part of the reason for this is that we were deliberate to include hospitals where underrepresented populations are treated. Unfortunately, we didn't do as well regarding gender inclusion; only 28% of patients in the trial were women, even though the goal was 35%. It turns out that it is not uncommon for women to be underrepresented in PAD trials, and this remains a challenge that we need to solve.

Prof. Saratzis: There are several frameworks and tools that one can use to recruit hard-to-reach and underserved populations in PAD randomized studies. These must be carefully considered when designing the trial and writing up protocols/recruitment pathways.

With the wisdom only afforded by hindsight, if you were to redesign your trial, what changes would you make, and why? How might these changes have affected the outcome?

Prof. Saratzis: With regard to BEST-CLI and BASIL-2, I would personally have tried to address heterogeneity in terms of anatomy. One could potentially stratify based on the anatomic segment affected. Furthermore, I feel that we urgently need to figure out mechanisms that will allow us to deliver large international randomized trials supported via public funders. This would ensure better representation of underserved groups and more efficient recruitment.

Dr. Farber: In an ideal universe, we should have had a concurrent registry that included every patient with CLTI at every site. That would have been ideal because issues of generalizability would have been easier to resolve. In addition, we would have collected angiograms, expanded our case report forms to collect more information, and enrolled more patients in cohort 2.

Dr. DeRubertis: In designing an IDE trial, we struggle with setting up the trial in such a way that the properties of the device can be isolated and examined while still including treatment strategies and patient populations that reflect real-world practice. How this balance is established can affect enrollment curves and ultimate trial success, as well as applicability to our patients once a trial has been completed. In the LIFE-BTK trial, the length of the scaffold and other factors related to potential compressive forces in the distal lower leg and ankle region caused us to establish inclusion criteria limiting the lesions to the proximal two-thirds of the lower leg. Although this was appropriate for the randomized trial and clearly allowed us to establish the profound device

efficacy versus PTA in this region, there remain questions regarding its performance in longer lesions or lesions located closer to the ankle region. These are all questions that we will of course explore after full commercial launch through the use of postmarket studies.

Given the challenges of enrollment in large-scale trials in this severe disease, what might a feasible next trial explore or seek to answer?

Dr. Farber: The next trials should explore how we can lower mortality in patients with CLTI. Perhaps we should be looking more for coronary artery disease in our patients and treating it more aggressively, we need to better characterize arterial runoff or distal foot perfusion and perhaps create a perfusion index to better predict outcomes of the various revascularization therapies. Finally, we need to better define which endovascular techniques work best for what anatomy and for which patients.

Prof. Saratzis: Randomized trial design should be as pragmatic as possible, accounting for local preferences where feasible and supporting health care professionals to randomize as many patients as possible. Also, data collection forms must be designed in a way that they are simple enough (but not simplistic) for research staff to complete in an efficient manner. Furthermore, investigators must be aware of existing equality, diversity, and inclusivity frameworks when designing their study and delivering the research at recruiting sites. The National Institute for Health and Care Research in the United Kingdom provides several examples and frameworks/tools to support recruitment in randomized studies, especially in difficult to reach populations. Finally, there must be a culture change in the vascular world overall. All patients should be given the opportunity to take part in randomized studies. It is our professional duty to help produce high-quality research, the findings of which can be extrapolated to routine clinical care. We now have several randomized, high-quality studies funded in the PAD environment, and clinicians must overcome equipoise issues, putting their own preferences and biases to the side.

Dr. DeRubertis: Moving forward, we will need to show a high degree of creativity in designing CLTI trials. The complexity of this patient population and the heterogeneity of the disease patterns makes it difficult to design trials that accurately capture the disease process and ultimately establish best treatment algorithms. I foresee an increasing use of adaptive trial designs, randomized trial registries, and target trial emulation techniques, as well as increased use of large data sets and machine learning to help solve some of these problems.

Dr. Geraghty: I'd love to see inclusion of patients with advanced calcific disease, ESRD patients, and more complex wounds. This will require control angiography for adequate biologic response assessment in IDE trials, and greater protocolization and consensus of wound care. Enrollments would really accelerate, and the trial results would be more broadly representative of our daily practice. ■

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Disclosures
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Dr. Farber: Consultant to Sanifit, LeMaitre, Biogencell, iThera, and DialysisX.
Dr. Geraghty: Advisory board member and stock/stock options holder in MedAlliance/Cordis, Aveera, Protexa, and Pulse Therapeutics.
Prof. Saratzis: Receives honoraria and lecture fees from Shockwave, Abbott, and Cook; consultant to Shockwave, Abbott, and Cook; receives educational grant support from Cook; receives research funding from Shockwave, Abbott, Boston Scientific, and Angiodroid.