PANEL DISCUSSION

Considering the Next Horizon of CLTI Trials

With BEST-CLI and BASIL-2 now complete, physicians contemplate the next phase of CLTI trials, including areas of focus and predictions for the most clinically impactful data.

With Marianne Brodmann, MD; Kumar Madassery, MD, FSIR; Sabine Steiner, MD; Zola N'Dandu, MD, FSCAI; and Matthew Menard, MD

Marianne Brodmann, MD
Division of Angiology
Medical University Graz
Graz, Austria
marianne.brodmann@medunigraz.at

Kumar Madassery, MD, FSIR
Associate Professor, Vascular Interventional Radiology
Rush University Medical Center
Chicago, Illinois
Director, CLTI Preservation Program
Rush Oak Park Hospital
Oak Park, Illinois
kmadassery@gmail.com

Sabine Steiner, MD
Head of Angiology
Department of Internal Medicine II
Medical University of Vienna
Vienna, Austria
sabine.steiner@yahoo.com

Zola N'Dandu, MD, FSCAI
Interventional Cardiologist and Endovascular Specialist
Ansaarie Cardiac and Endovascular Center of Excellence
St Augustine, Florida
East Palatka, Florida
zola.ndandu@gmail.com

Matthew Menard, MD
Associate Professor of Surgery
Harvard Medical School
Codirector, Endovascular Surgery
Brigham and Women's Hospital
Boston, Massachusetts
mmenard@partners.org

With BEST-CLI, BASIL-2, and others complete, what do you see as the next clinical trial horizon for chronic limb-threatening ischemia (CLTI)/ critical limb ischemia (CLI)?

Prof. Brodmann: There are currently trials underway evaluating drug-coated balloon (DCB) with either paclitaxel or limus in the below-the-knee (BTK) area. ELITE-BTK is a new trial of a drug-eluting bioresorbable scaffold in the BTK space, and it will be the second-largest trial after LIFE-BTK.

After that, I would love to see a trial studying paclitaxel DCB versus limus DCB in BTK and CLTI, as well as a trial of DCB versus plain old balloon angioplasty versus bioresorbable scaffold in BTK disease and CLTI patients.

Prof. Steiner: With BEST-CLI and BASIL-2 now complete, the next clinical trial horizon for CLTI will likely focus on refining personalized treatment strategies, optimizing drug-based and adjunctive therapies, and integrating hybrid approaches that combine surgical and endovascular techniques. Future studies should emphasize patient-specific decision-making, identifying which subgroups benefit most from each treatment strategy based on anatomic, functional, and frailty assessments.

Additionally, there is an increasing need for trials assessing the role of vessel preparation and drug-eluting technologies, as well as systemic therapies—including anti-inflammatory agents and regenerative medicine—in improving outcomes for CLTI patients. Unlike other cardiovascular diseases, such as heart failure and acute myocardial infarction, disease-modifying therapies have failed to reduce the high mortality rates in CLTI, underscoring the urgent need for further research. Beyond revascularization, wound healing remains a critical factor in CLTI management, and new trials should explore adjunctive therapies, including regenerative stem cell and gene therapy and advanced wound care techniques. Deep venous arterialization has emerged as a promising option for patients with no conventional revascularization targets, and future trials should investigate its long-term patency, impact on collateral growth, limb salvage rates, and patient selection criteria.

Dr. Madassery: We have seen quite a bit of information emerge from these large trials, which set out to answer very important questions that we have historically gone back and forth on in the peripheral artery disease (PAD) space.

To be honest, I do not think we have learned a lot we did not already know. Consider BEST-CLI; I think most vascular specialists know that for infrainguinal long-segment occlusions, a native vein bypass still has the best long-term patency rates. That doesn't mean we haven't had great studies using drug-based technologies over the years that have gotten us excellent patency up to 5 years. However, from a global view, a good autologous bypass with an experienced surgeon in a relatively healthy/younger patient still needs to be prioritized. That being said, with a strong collaborative system and experienced interventionalists, an endovascular revascularization is often still a great first option that should not "burn bridges." There are nuances to good, safe interventions where you can be cognizant of keeping options open for other approaches. In a high-level practice, most operators do not see this problem. At the same time, many operators find that endovascular interventions after surgery can be difficult for a multitude of reasons. Other considerations to keep in mind include operator-specialty potential biases and drug-based technology use, but it is important to note that these are only considerations, not faults.

In BASIL-2, we saw higher numbers of dedicated interventionalists, a likely sicker patient population, and more focus on infrapopliteal reavascularization, with many having prior revascularizations. We know that infrapopliteal bypass and repeat infrapopliteal interventions tend to carry unfavorable outcomes. There was considerable heterogeneity in the trial, and we cannot equally compare BEST-CLI and BASIL-2 or point to one or the other as the best answer.

What we did see, especially in BEST-CLI, is that even in trials, many patients are failing to receive the best medical management therapies that could help prevent the ultimate consequence for CLI/CLTI and PAD patients in general: increased mortality compared to most other chronic progressive disease. I use the term "arterial cancer" to help patients understand the seriousness of the progression of PAD stages. We must do better to manage the underlying risk factors and other comorbidities. Although not easy in this patient population, we all need to improve our education and communications with patients, families, and colleagues.

It is hard to imagine the next best trial horizon in CLTI. Optimistically, a future clinical trial would incorporate equal representation from multiple specialties, including proven high-volume and outcomes-based interventionalists and surgeons. And, it should incorporate current innovative technologies and approaches. In a perfect scenario, all patients would be evaluated, staged, and classified in a similar fashion and then virtually evaluated by a multidisciplinary group that can help guide the process instantaneously with an agreed-upon course of treatment approaches. This would be difficult to standardize, but with so many ways to deal with lesions, chronic total occlusion accesses, and tools, for example, how else can we ever hope to get clear answers?

There is so much variability in experience and capabilities locally and globally, regardless of specialty, that there is no other way to standardize the process. It would also require a global community of patients and operators, which is not an easy feat. In the end, this may be difficult and not attainable, but if we want to consider the perfect study, we have to understand the limitations.

Dr. Menard: Although BEST-CLI, BASIL-2, and BASIL-3 have completed enrollment, we are continuing to unpack the robust amount of data contained in the data set. We are on target to publish up to 50 additional

papers of secondary analyses beyond the main results. These are incredibly exciting additions to our understanding of the study results, as they begin to tell the story of what the trial has been able to reveal. It has been gratifying to have these studies be carried out by the folks that did the hard work of enrolling and completing the trial, and in many cases, investigators have been able to dig in to areas in which they have specific expertise.

With regard to the future, I am hopeful that the BEST-CLI and BASIL trials are just the beginning, as there are so many important clinical questions remaining that need answering. Several areas that I think need specific and focused attention include clarifying just how much perfusion is needed for a given CLI patient. For instance, it would be a major clinical advance if we could determine how much perfusion improvement will get a patient durably free of rest pain versus how much another patient needs to heal their fifth toe ulcer or third toe amputation wound. We need to better understand the role and outcomes of below-the-ankle revascularization, both open and endovascular, and further characterize the short-, intermediate-, and long-term outcomes of aggressive inframalleolar interventions. We are just now beginning to understand the implications of calcium in general, but of particular interest is how we should be thinking about it at the ankle, forefoot, and digital level. The longer-term goal is to begin to substantively understand the relationship between different presenting patterns of arterial occlusive disease and the outcomes of different treatment strategies. In other words, the development of more sophisticated anatomic prediction models, akin to the SYNTAX scoring system in regular use to help guide percutaneous coronary intervention (PCI) versus coronary artery bypass grafting decision-making, remains a significant unmet need.

Another area ripe for future research is a better understanding the interplay between medical therapy and revascularization options. On the heels of BEST-CLI and BASIL-2/3, COMPASS, VOYAGER, and FOURIER, in combination with the explosion of evidence supporting the utility of GLP-1 agonists and PCSK9 inhibitors, sorting out which combinations of medications are most beneficial following which revascularization strategies is an exciting challenge and one that both demands and lends itself to robust collaboration between and within the fields of vascular surgery, vascular medicine, interventional radiology, and interventional cardiology. Certainly, continuing to develop the evidence base that will further elucidate which endovascular options are best for which patients and occlusive patterns is of high priority. Similarly, we are doing more and more hybrid procedures, both basic and creative, and yet, we have very little data to support our collective hunch that this trend makes sound clinical sense. As such, defining what combinations of complementary tools make the most sense for what clinical scenarios based on robust and durable data is another unmet need.

Finally, we are all awaiting the results of SWEDEPAD 1 and 2, in part because of their ground-breaking role in revealing the utility of registry-based randomized controlled trials going forward. Such a trial construct might become a cornerstone in future evidence generation, given the potential benefits in cost reduction, feasibility, and generalizability compared to the gold standard of randomized controlled trials.

Dr. N'Dandu: After the publication of landmark trials such as BEST-CLI, BASIL-2, LIFE-BTK, and PROMISE II, the treatment paradigm for CLTI is entering a new era of increasing focus on functional outcomes, as well as personalized treatment and novel technologies.[1-4] These pivotal studies have clarified critical aspects of revascularization strategy, including patient selection, anatomic complexity, and the role of comorbidities.[5] However, there are still unmet needs in the area of microvascular disease referred to as "no-option" CLTI, and in tailoring therapies to individual risk profiles.

Among the next generation of CLTI trials is the emergence of sirolimus-based therapies, which offer a promising alternative to paclitaxel for reducing restenosis with an improved safety profile.[6] Device innovation is also accelerating, with bioabsorbable scaffolds and temporary drug-eluting platforms designed to deliver targeted therapy while minimizing long-term inflammation or stent-related complications.[3] Simultaneously, interest in personalized antithrombotic strategies is increasing, with evolving regimens based on platelet function testing, pharmacogenomics, and individualized bleeding risk. These efforts include a growing body of work combining antiplatelet and anticoagulant therapies in select high-risk CLTI populations to optimize thrombosis prevention without increasing bleeding events.[7]

In the intravascular imaging space, newer-generation intravascular ultrasound (IVUS) and optical coherence tomography (OCT) systems are offering improved resolution, plaque characterization, and vessel sizing capabilities.[8,9] IVUS-guided interventions have been associated with reduced restenosis and improved stent expansion in peripheral interventions, and OCT enables high-resolution visualization of plaque morphology and calcification patterns.[8,9] Advanced MRI-based plaque imaging may further inform preprocedural planning, especially in complex, calcified lesions.[10] This improved lesion

characterization is increasingly used to guide the choice of atherectomy, intravascular lithotripsy, or other vessel preparation techniques before definitive treatment.[11] These modalities allow interventionalists to make real-time decision-making in selecting appropriate devices based on lesion compliance, eccentricity, and calcium burden. This approach is especially valuable in tibial and inframalleolar interventions.

Artificial intelligence (AI)–assisted imaging and wearable monitoring technologies are currently being researched for their ability to detect restenosis earlier, noninvasively assess limb perfusion, and guide personalized follow-up schedules.[12] These digital tools, combined with pharmacologic and device-based advances, are reshaping how we define success in CLTI, not only in limb salvage and patency but also in mobility, quality of life (QOL), and patient-centered outcomes.

Looking ahead, the convergence of precision-based therapies, real-world registries, intravascular imaging, and multidisciplinary care models offers an opportunity to close long-standing gaps in CLTI treatment. These innovations hold the potential to make limb preservation more effective, more equitable, and more sustainable.

Which data would have the most impact on CLTI practices locally and worldwide?

Dr. Madassery: Data relevant to the patient demographics inherent to one's practice. We see a lot of data that is not applicable to one's practice; however, when we can find ways to gather large global data sets, and if we can utilize advanced data processing and estimations (eg, with AI), then we may be able to better predict and talk to our patients about what they can really expect. Data on amputation-free survival and mortality are usually the biggest factors people care about; however, more robust understanding of who may be likely to get repeat surgeries/interventions, thrombosis, time to wound healing, limb loss, and cost predictions could all be additional, highly sought-after data.

Prof. Steiner: Given the complexity and variability of CLTI, real-world evidence from global registries will be essential for understanding long-term outcomes, cost-effectiveness, and disparities in access to care. Additionally, registry-based randomized controlled trials could offer a valuable approach to generating high-quality data while enabling broad patient inclusion and pragmatic study designs. These trials can provide critical insights into treatment durability, limb salvage rates, functional recovery, and QOL, while also facilitating economic analyses of different therapeutic strategies.

Equally important is the recognition of palliative care for patients with severe comorbidities who may not be candidates for aggressive revascularization. Research should explore the integration of palliative strategies—including optimal wound management, pain control, and shared decision-making—to enhance QOL.

Furthermore, understanding global practice patterns and addressing treatment disparities will be critical to shaping the future of CLTI care. Ensuring equitable access to innovations in revascularization and adjunctive therapies will be key to improving outcomes for a diverse patient population.

Dr. N'Dandu: Integrating comprehensive, high-quality data is crucial to improving outcomes in CLTI. The most impactful data will incorporate epidemiologic trends, health system performance metrics, treatment outcomes, and social determinants of health. Recent analyses of Medicare data estimate that hundreds of thousands of patients are diagnosed with CLTI annually, with its prevalence continuing to rise.[13] These data enable health care systems to identify at-risk populations and inform targeted prevention and screening strategies. This type of real-world evidence can help close the gap between clinical trial populations and the diverse, often medically complex patients we encounter in daily practice, moving beyond the limitations of narrowly selected trial cohorts.

Health system metrics are equally vital for identifying gaps in care, particularly in underserved communities. Real-world treatment outcomes, tracked through registries like the Vascular Quality Initiative,[14] Outpatient Endovascular Intervention Society, and National Cardiovascular Data Registry, provide crucial benchmarks on amputation rates, limb salvage, and overall survival. These registries also drive quality improvement efforts and evidence-based practice. Additionally, social determinants (ie, income, education level, and geographic location) play a critical role in CLTI outcomes. Disadvantaged patients often face significantly higher rates of delayed care and major amputation.[15] A global, data-driven approach that combines these insights can enhance early detection, ensure equitable access to care, and improve limb preservation efforts worldwide.

Prof. Brodmann: Most impactful would be positive efficacy outcomes data from trials, such as what we saw with LIFE-BTK. These data provide support for using drug-eluting bioresorbable scaffolds BTK in CLTI patients.

Dr. Menard: It goes without saying that what strategies might work in one country might not be practical or applicable in others. As such, robust QOL and cost-effective-

ness data across different health care systems would be particularly helpful globally. On the other hand, detailed data on reinterventions and specific mechanisms of failure following both open and endovascular treatment would be very helpful to fully understand the impact of initial treatments.

Although immunologic modulation with drug elution is clearly efficacious and has a central role in PAD, the role of limus drug therapy and to what degree it has a bright future remains to be clarified, particularly in countries where resources are thin. There remains a clear need for self-expanding stents BTK. And while it will be hard to do, systematic investigation of each component of endovascular care, to show its relative role and value, is long overdue. Granular comparative data are routinely investigated and gathered in the PCI space, and it should be the standard we aspire to in the peripheral space as well. With better understanding in hand, utilizing artificial intelligence and big data registries may then afford the opportunity to match individual clinical and anatomic risk profiles with specific open surgical and endovascular treatment paradigms in a way that represents the ideal world of personalized medicine. While this is only a dream at the moment, it is a direction I believe we can and should be headed toward. ■

1. Farber A, Menard MT, Conte MS, et al. Surgery or endovascular therapy for chronic limb-threatening ischemia. N Engl J Med. 2022;387:2305-2315. doi: 10.1056/NEJMoa2207899
2. Bradbury AW, Moakes CA, Popplewell M, et al. A vein bypass first versus a best endovascular treatment first revascularisation strategy for patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal revascularisation procedure to restore limb perfusion (BASIL-2): an open-label, randomised, multicentre, phase 3 trial. Lancet. 2023;401:1798-1809. doi: 10.1016/S0140-6736(23)00462-2
3. Varcoe RL, Parikh SA, DeRubertis BG, et al. Evaluation of an infrapopliteal drug-eluting resorbable scaffold: design methodology for the LIFE-BTK randomized controlled trial. J Soc Cardiovasc Angiogr Interv. 2023;2:100964. doi: 10.1016/j.jscai.2023.100964
4. Shishehbor MH, Powell RJ, Montero-Baker MF, et al. Transcatheter arterialization of deep veins in chronic limb-threatening ischemia. N Engl J Med. 2023;388:1171-1180. doi: 10.1056/NEJMoa2212754
5. Menard M, Jaff MR, Farber A, et al. Baseline modern medical management in the BEST- trial. J Vasc Surg. 2023;78:711-718.e5. doi: 10.1016/j.jvs.2023.05.006
6. Barco S, Sebastian T, Voci D, et al. Major adverse limb events in patients with femoro-popliteal and below-the-knee peripheral arterial disease treated with either sirolimus-coated balloon or standard uncoated balloon angioplasty: a structured protocol summary of the SirPAD randomized controlled trial. Trials. 2022;23:334. doi: 10.1186/s13063-022-06242-8
7. Bonaca MP, Bauersachs R, Anand SS, et al. Rivaroxaban in peripheral artery disease after revascularization. N Engl J Med. 2020;382:1994-2004. doi: 10.1056/NEJMoa2000052
8. Divakaran S, Parikh SA, Hawkins BM, et al. Temporal trends, practice variation, and associated outcomes with IVUS use during peripheral arterial intervention. JACC Cardiovasc Interv. 2022;15:2080-2090. doi: 10.1016/j.jcin.2022.07.050
9. Spiliopoulos S, Kitrou P, Katsanos K, Karnabtidis D. FD-OCT and IVUS intravascular imaging modalities in peripheral vasculature. Expert Rev Med Devices. 2017;14:127-134. doi: 10.1080/17434440.2017.1280391
10. Csore J, Roy TL, Wright F, Karmonik C. Unsupervised classification of multi-contrast magnetic resonance histology of peripheral arterial disease lesions using a convolutional variational autoencoder with a Gaussian mixture model in latent space: a technical feasibility study. Comput Med Imaging Graph. 2024;115:102372. doi: 10.1016/j.compmedimag.2024.102372
11. Chong R, Sebastian E, Katib N, et al. Intravascular lithotripsy in infra-popliteal peripheral artery disease. J Cardiovasc Surg (Torino). 2024;65:454-459. doi: 10.23736/S0021-9509.24.13148-5
12. Callegari S, Romain G, Cleman J, et al. Long-term mortality predictors using a machine-learning approach in patients with chronic limb-threatening ischemia after peripheral vascular intervention. J Am Heart Assoc. 2024;13:e034477. doi: 10.1161/JAHA.124.034477
13. Barnes JA, Eid MA, Creager MA, Goodney PP. Epidemiology and risk of amputation in patients with diabetes mellitus and peripheral artery disease. Arterioscler Thromb Vasc Biol. 2020;40:1808-1817. doi: 10.1161/ATVBAHA.120.314595
14. El Khoury R, Wu B, Kupiec-Weglinski SA, et al. Applicability of the Vascular Quality Initiative mortality prediction model for infrainguinal revascularization in a tertiary limb preservation center population. J Vasc Surg. 2022;76:505-512.e2. doi: 10.1016/j.jvs.2022.03.013
15. Gallagher M, Bonilla C. Health disparities across the spectrum of amputation care: a review of literature. Phys Med Rehabil Clin N Am. 2024;35:851-864. doi: 10.1016/j.pmr.2024.06.006

Disclosures
Prof. Brodmann: Consultant to R3 Vascular.
Dr. Madassery: Consultant to Abbott, Philips, Penumbra, Cook Medical, Asahi Intecc, and Shockwave Medical; medical advisory board, Cordis.
Prof. Steiner: None.
Dr. N'Dandu: Consultant to Abbott, Boston Scientific, BD Interventional, LimFlow, Gore & Associates, and Terumo; Site Primary Investigator for PROMISE II trial.
Dr. Menard: Funding support for BEST-CLI from the National Institutes of Health, NovoNordisk Foundation; scientific advisory board, Janssen, Anges, and Regeneron.