ROUNDTABLE DISCUSSION

Next Horizons in BTK Disease Research

Priorities for CLI/CLTI research, where progress needs to be made regarding limb salvage disparities, the role of artificial intelligence in individualizing care, and what the multidisciplinary care team of the future should look like.

Carlos Mena-Hurtado, MD, FACC, FSCAI
Department of Internal Medicine
Section of Cardiovascular Medicine
Co-Director, Vascular Medicine Outcomes Program
Director, Peripheral Vascular Disease
Yale School of Medicine
Yale University
New Haven, Connecticut
carlos.mena-hurtado@yale.edu

Kim G. Smolderen, PhD
Department of Internal Medicine and Department of Psychiatry
Section of Cardiovascular Medicine
Co-Director, Vascular Medicine Outcomes Program
Yale School of Medicine
Yale University
New Haven, Connecticut
kim.smolderen@yale.edu

Mark J. Portou, PhD, FRCS
Consultant Vascular Surgeon
Lead for Peripheral Limb, Diabetic Foot, and Amputation
North-Central London
Royal Free London NHS Foundation Trust
London, United Kingdom
m.portou@nhs.net

Samantha D. Minc, MD, MPH, FACS, FSVS
Associate Professor
Division of Vascular and Endovascular Surgery
Department of Cardiovascular and Thoracic Surgery
WVU School of Medicine
Adjunct Associate Professor
WVU School of Public Health
West Virginia University
Morgantown, West Virginia
samantha.minc@wvumedicine.org

Recent years have seen a surge in interest in critical limb ischemia (CLI)/chronic limb-threatening ischemia (CLTI) and amputation prevention, both within and outside of the medical community, but the work is far from over. In your opinion, what are the top three priorities for CLI/CLTI research in the next several years?

Drs. Mena-Hurtado and Smolderen: Amputation rates have remained relatively stable over the years. Prevalence of CLI/CLTI is increasing and is increasing fastest in younger populations presenting with severe disease and a cluster of comorbidities (eg, diabetes, obesity, renal disease, mental health disorders). Individuals from vulnerable socioeconomic backgrounds and those with minority backgrounds are disproportionately affected. Our current prevention, detection, and treatment programs have not been able to counter these trends. This goes to show that new efforts are needed toward the following:

- Investments in the development of prevention, detection, and treatment programs that look at

this condition from a "whole-person perspective," considering social determinants of health that are the main drivers of developing this condition in the first place. This requires a paradigm shift, focusing not only on the leg but the whole person.
- Instituting national surveillance programs for amputation rates, as we know there is great variability in rates depending on geography, institutions, and providers that offer CLI/CLTI care; racial and ethnic background; and socioeconomic status. We need an accountable system governed by a multistakeholder, neutral body.
- Develop data-driven, validated, value-based care models to reduce amputation rates and readmission rates that can inform reimbursement criteria, as well as criteria for centers of excellence for offering CLI/CLTI care.

You asked us about the top three priorities, but we would like to add a fourth, which is a systematic effort in education and awareness not only at the level of the community, patients, and their families and caregivers but also the wide range of clinicians, including mid-level providers, who interact with patients at risk of developing CLI/CLTI so they are more aware of symptoms and risk factors and can be more proactive in detecting and preventing disease escalation.

Dr. Portou: In terms of CLTI research, I think all areas are priorities! Seeing as I have to choose, something I feel is an underappreciated consequence of CLTI is the lack of limb function restoration after technically successful revascularization. We can salvage the limb, prevent amputation, and heal wounds through an ever-expanding repertoire of adjuncts and techniques; however, the patients do not regain premorbid functional capabilities. Animal studies have demonstrated a clear histologic change in ischemic muscle, with the ultimate replacement of functioning sarcomeres with fibroadipose tissues. I would like to understand—through the CLTI patient's journey from presymptomatic through intermittent claudication and finally CLI—when the optimum time is to revascularize to preserve muscle function. I suspect it will be much earlier in the symptomatic phase than we appreciate. This may sway the risk versus benefit decision-making between conservative management and intervention in the early stages of the condition.

The next priority as an endovascular enthusiast relates to the ongoing debate between an endovascular- versus open-first strategy in CLI/CLTI management. With the recent publication of the BASIL-2 trial[1] suggesting an endo-first approach is superior, in apparent contradiction to the BEST-CLI trial,[2] there is clearly yet to be a totally definitive answer. Although I can understand fully the position from both sides of the argument, and ascertaining which method is better merely aims to guide best practice, I feel it is time to start thinking differently about the question.

To state the obvious, open surgery by its nature removes "the problem" by joining healthy artery to distal healthy artery. However, endovascular surgery attempts to repair the native vessel and restore flow through the existing diseased or occluded anatomy. As a community, we should continue asking how we can better and more durably restore native vessel patency and reduce thrombogenicity to improve the outcomes achieved through either surgical bypass or current best arterial "territory specific" endo practice. Achieving this will require a mind shift toward aggressive treatment of *every* disease level using whichever adjunctive technology best addresses each specific lesion and, if necessary, combining them within the same limb (ie, a "lesion-specific" approach). Likewise, simultaneously adopting a tailored individualized perspective to antiplatelet and anticoagulant usage is necessary to optimize platelet inhibition and reduce thrombotic risk.

Finally, it remains an inconvenient truth that long-term survival of CLTI patients is extremely limited. Despite ever-improving recognition and minimally invasive techniques for limb salvage, a majority of CLTI patients are still dead at 5 years. It is uncontroversial to make the medical optimization of diabetes, respiratory conditions, and cardiovascular risk an immediate priority. A subject close to my own heart is recognition of the pathologically proinflammatory condition of diabetes and, further to this, the consequences of all states that lead to chronic endothelial inflammation. Many of the most successful cardiovascular pharmacotherapies (eg, statins) have potent innate immune anti-inflammatory effects. The development of targeted pharmacologic agents to ameliorate the effects of hyperglycemia, hypertension, and hypercholesterolemia (that all lead to innate immune–mediated proinflammatory endothelial damage) may just help slow the progression of atherosclerosis. Ultimately, we must strive to put ourselves out of business.

Dr. Minc: Priority areas for CLTI/amputation prevention research include (1) implementation science, (2) community-engaged research, and (3) patient-centered outcomes research. These research areas are of particular importance because they not only help improve our understanding of human behavior and disease prevention but also educate, engage, and empower clinicians and patients to be a part of the process. This ensures that our research will be relevant to our patient population and provides a platform for transformational research that produces high-impact, sustainable results.

There is increasing focus in recent years on identifying the disparities present in the rate of amputation and/or worse clinical outcomes among racial/ethnic minorities and low-socioeconomic populations. What are key knowns and unknowns regarding disparities in limb salvage care and outcomes?

Drs. Mena-Hurtado and Smolderen: We know that amputation rates are much higher in Black/African American, Hispanic, and Native American populations compared with White patients. Severe CLI/CLTI in these groups also presents at a younger age, often with a lower socioeconomic status profile (eg, lowest quartile of household income) and other comorbidities (eg, diabetes, obesity, mental health disorders, renal disease). We are just beginning to document the mechanisms underlying these disparities. By focusing on exposures to trauma, distress experiences in individuals' communities, and barriers in accessing to care, we can fill in a more complete picture. We have not studied the role of racism, intergenerational trauma, impact of these factors and epigenetics, the role of diet and food security, access to green zones where communities can exercise, the role of education, and the impact of policy measures that work against maintaining one's health, just to name a few potential mechanisms. Most likely, we must uncover the multifactorial story and get at the roots of the problem if we want to eradicate these inequities.

As we uncover these mechanisms, we need to be aware of the need to enhance education experiences of those who will be interacting with CLI/CLTI patients. Trauma-informed care is novel, and understanding stressors and their impact on biological mechanisms and educating on social determinants of health will require renewed efforts of training and redesigning care to take these aspects into account as we are caring for this population. In addition, we need to diversify the workforce caring for this population, making sure we provide culturally sensitive care and recognize the humanity in our patients as they go through this profoundly impactful disease.

Dr. Minc: As your readers are aware, amputations are a highly preventable complication of CLTI. Eighty-five percent of amputations are preceded by a foot ulcer that can be treated with timely podiatric and vascular intervention. Due to their highly preventable nature, amputation disparities are an indicator of inequities in health care access and quality, as well as nonmedical factors such as food security, transportation, and housing stability. A significant body of literature describes the racial and ethnic disparities in amputation rates for CLTI and diabetes. Even after controlling for risk factors such as socioeconomic status, comorbidities, and advanced disease, Black/African American and Hispanic/Latine patients are two to four times more likely than White patients to undergo major amputation for CLTI/diabetes. More troubling, they are also more likely to undergo primary amputation (ie, amputation without attempt at revascularization). Similar findings have been reported in Native American and rural populations, although additional research in these populations and other marginalized groups is warranted. In addition, there is emerging literature demonstrating that a significant risk factor for amputation is intersectionality: the theory that individuals' multiple identities within a social system compound and exacerbate experiences of ill health. An example of the effect of intersectionality on amputation disparities is the finding that rural Black/African American patients have a higher risk of primary amputation than their urban Black/African American counterparts and a higher risk of amputation for diabetic foot ulcer than would otherwise be expected if the risk of amputation associated with rural residence and Black/African American race were simply additive.

The biggest unknown in amputation disparities research is why these disparities happen. Up to this point, the majority of CLTI disparities research has been focused on quantifying disparities. Building an actual understanding of the key drivers of these disparities is a critical next step to inform strategies to effectively reduce them.

Dr. Portou: The association between increased amputation rates in individuals from African American and Hispanic ethnicities and from low socioeconomic incomes is well recognized in the United States. Factors such as reduced access to health care and a greater severity of disease at presentation have been identified as compelling factors in explaining the disparity. However, the same broad categories of risk factors and comorbidities are common to all ethnic groups. It is known that significant barriers to effective risk factor management exist to prevent disease progression in the most at-risk ethnic groups.

What is unclear to me is whether the increased rate of major amputation can be entirely explained by these nonbiological factors alone or if there are also differences between ethnic groups in the way diabetes and atherosclerotic disease manifest that perhaps lead to a more aggressive microvascular-type phenotype. If so, how can we better develop strategies to pharmacologically target these?

What about the differences observed in a society with an intended "equitable" health care system such as the United Kingdom (UK)? In England, a clear north-south

divide exists, with a greater prevalence of revascularization and major amputation identified in the north. This was in spite of the observation that higher prevalence of diabetes, hypertension, and hypercholesterolemia was found in the south. However, populations that live in the north had a greater degree of social deprivation, coronary heart disease, and, importantly, smoking.

How do we make the connection between these data and actionable means of reduction in disparities? What are the next steps?

Dr. Minc: As mentioned previously, much of the research on CLTI disparities has been focused on proving and quantifying disparities rather than explaining why they exist. To effectively reduce disparities, we must focus on projects that use research methods to explain findings and generate actionable plans to address them. These methods include qualitative approaches (interviews, focus groups), mixed methods (integrated quantitative and qualitative research to build a complete picture of the issue), patient-centered outcomes research, and community-engaged research. It is only by gaining a complete picture of the problem and engaging the people affected by it that we will be able make effective, sustainable progress in reducing disparities.

Dr. Portou: A recognition of the fact the status quo is not working. Irrespective of the possibility of different biological susceptibility, health promotion initiatives must target the most at-risk populations. An uncomfortable recognition of the societal and "structural"- or "institutional"- based barriers to effective early diagnosis, treatment, and risk factor modification needs to be coupled with solutions that drastically acknowledge and offer practical solutions to these barriers.

For instance, what can explain the link between social deprivation and major amputation despite the free health care for all in the UK National Health Service? There's no evidence to suggest the quality or availability of health care differs between regions of England, but there is a strong association between major amputation, social deprivation, welfare claims and unemployment, and increased smoking prevalence. Unemployed individuals smoke significantly more than those employed. If this phenomenon is extrapolated out to other risky and unhealthy behaviors such as obesity, poor nutritional habits, and lack of exercise, a possible causal link starts to emerge. Reducing the disparities in this situation is therefore beyond the reach of health providers and national services and in the hands of politicians.

Drs. Mena-Hurtado and Smolderen: The three priorities we outlined before are a start. Studying the mechanisms listed above and thinking of CLI/CLTI as a systemic chronic disease is another key direction to follow. We need to understand that this condition impacts the most vulnerable communities of our society and highlight that this is a larger societal problem because of the choices we make as to how we organize access to education, healthy food, and healing environments and acknowledge the burdens that our socioeconomic systems put on the most vulnerable groups of our society. This type of thinking involves a multistakeholder approach, advocacy, research, and working together with all involved in delivering care for these patients. It also requires communities, their leaders, and decision-makers at the health system, state, and national levels to invest in programs to tackle the larger issues. We need to look at whole-person care and prevention as an investment into the future to address core mechanisms that lead to CLI/CLTI at their root causes, not just when patients show up with an endangered limb and face amputation.

What potential do you envision for artificial intelligence (AI) and machine learning in CLI/CLTI care?

Dr. Portou: I believe there is enormous potential for AI in CLTI management. To start, the ability to automatically identify individuals and offer medical optimization of secondary cardiovascular protection would remove the subjectivity and potential for human bias. Using existing data sets such as general practice or hospital-based records, those who might otherwise not appear on the radar of a vascular specialist or are presymptomatic would be more effectively targeted.

In those who presented with established disease, I believe AI may have potential in aiding vascular specialists in improving the outcomes of endovascular interventions through assisted recognition of lesion-specific morphologies and algorithms to help decide best modality and method of treatment. Likewise, success of intervention may be more completely assessed at the time of the procedure.

Dr. Minc: Machine learning/AI is an extremely useful tool for CLI/CLTI researchers. These approaches use predictive rather than explanatory modeling (which physicians are often more familiar with) and can take a multitude of factors into account to predict outcomes that might not be obvious otherwise. It is important to remember that these tools are exploratory; therefore, results must be carefully interpreted by experienced clinicians, and additional prospective research must be performed to confirm findings. In my preliminary

research, we performed geospatial analyses using Bayesian modeling (an approach related to machine learning) to predict amputation hot spots on a highly granular level in a rural state. This approach was crucial to successfully identify an amputation hot spot, as rural areas have fewer people than urban areas and traditional mapping models that work well with large numbers cannot be applied in these scenarios. By using this predictive method, we were able to identify a cluster of zip codes at higher risk for amputation than the rest of the state. We then performed multivariable analyses and qualitative research (via focus groups and interviews with people who experienced amputations and their clinicians) to better understand and confirm our findings.

Drs. Mena-Hurtado and Smolderen: We can definitely see a role for AI or machine learning to inform our value-based designed care and use more points of information to predict who will be at the highest risk of developing CLI/CLTI or facing amputations to prevent these outcomes from happening in the first place, so that more aggressive risk management and support can be provided early on.

What do you currently use or have available to guide individualized patient care, and what could/should be the role of AI in this?

Dr. Minc: At this point, the most thoroughly vetted tool to approach patients with CLTI is the Wound, Ischemia, and foot Infection (WIfI) system, which I use as a framework to evaluate every CLTI patient I see. WIfI provides a thorough, rational, step-by-step approach to properly evaluate wound severity, extent of infection, and perfusion status to help determine the most important next step for patient care. It also helps guide discussion with patients and set realistic goals and treatment plans. With regard to AI/machine learning, we know that CLTI patients are complex and have multiple variables that must be considered when managing them. As such, directing future AI/machine learning to adapt precision medicine models—which can guide treatment algorithms based on a patient's unique characteristics—to CLTI patients would be very useful.

Drs. Mena-Hurtado and Smolderen: Unfortunately, given the heterogenicity of patients' clinical presentation together with their background and comorbidities, the current scoring systems and approaches miss one or other clinical case scenarios and do not take this diversity into account. What is needed is a detailed review of the existing clinical evidence, such as BEST-CLI, together with an understanding of the knowledge gaps to generate new, inclusive, comprehensive ways to identify and treat patients with CLI/CLTI. There must be a multistakeholder commitment to these efforts, particularly from our industry partners who now understand that our efforts as a medical community cannot only be focused on device-specific research—especially when many of those devices lack adequate clinical evidence derived from the diverse populations we serve on a day-to-day basis.

Dr. Portou: I'd like to think all treatment decisions we make are completely individualized. Fundamentals such as the decision to intervene versus conservative management are made on the basis of a holistic patient assessment of risk versus benefit and patient wishes. Treatment modality is determined through consideration of periprocedural risk, comorbidity, anatomic factors, previous interventions, and technical complexity. Scoring systems no doubt help in the risk stratification process. AI could have a role in this decision-making process through consideration of the large number of variables involved in complex real-life scenarios, not only in the simplified or single-question specific situations.

You have all been pioneers in the effort to raise awareness of CLI/CLTI and move the field forward. Drs. Smolderen and Mena-Hurtado, can you share the current status of the SCOPE-CLI trial? How do you hope to see the findings of this trial move the field forward in terms of patient care, and have you identified any gaps wherein further research needs to be pursued once this trial has concluded?

Drs. Mena-Hurtado and Smolderen: Half of the patients (a cohort of 400 out of 816) are enrolled into the study, with continued longitudinal follow-up on patient health status and different presentations of CLI/CLTI. The trial will reveal how patients' experiences of chronic wounds impact health status compared to those undergoing amputation, with a disease-specific instrument. In previous work, we only had access to generic health status information averaged across disease manifestations, which does not tell us a lot regarding patients' individual experiences; we believe this information will directly inform care and shared decision-making for care of patients and clinicians.

Dr. Portou, how do current standards for screening/early detection of CLI/CLTI in the UK need to change?

Dr. Portou: The UK approach to CLTI is reactive rather than proactive. The cornerstone of management is treatment of established, often advanced, disease.

Even with the most severe symptoms, there can be a significant delay in referral to vascular specialists. I think this partly reflects the fragmented nature of the health service and arbitrary barriers between primary and secondary care. The Vascular Society of Great Britain and Ireland's Peripheral Artery Disease (PAD) Quality Improvement Framework and subsequent financial incentivization (Commissioning for Quality and Innovation) initiatives are specialty-led interventions to help raise and standardize quality of care and reduce variation and waiting times across the country for PAD, although they're targeted at the vascular community in secondary care. While they are critical and welcome pathways for improving outcomes in PAD management across the nation, there is still a complete reliance on the knowledge and recognition of primary care clinicians. Sadly, conditions such as coronary artery disease (CAD) and cerebrovascular disease (CVD), while still noncancer related, have a higher profile in the national consciousness.

Given the significant overlap of disease burden between individuals that present with CAD or CVD and those with PAD, I believe an opportunity exists to raise the profile of PAD and subsequently CLTI by targeting individuals with these related conditions, and likewise, patients with renal disease and diabetes.

Overall, we need to strive in the UK for earlier intervention in PAD management, but an opportunity also exists to aggressively manage risk factors and optimize best medical therapy in the early symptomatic populations. Supervised exercise programs for claudicants are much talked about but clearly drastically underfunded in the UK. An investment in health promotion and smoking cessation coupled with evidence-based best medial therapy and exercise programs would target the most at-risk populations and reduce overall cost to the taxpayer by reducing progression to CLTI.

Dr. Minc, can you tell us about your pilot program to prevent amputations in Pocahontas County, West Virginia (WV), and how you are approaching engaging with the community? What do you think is unique about this program and the resources you offer?

Dr. Minc: Our program is a 5-year National Institutes of Health–funded (K23) practice-based research project that uses a community-engaged approach to develop, implement, and assess an amputation prevention intervention in Pocahontas County, WV. This project builds on our preliminary research where we used a mixed-methods (ie, both quantitative and qualitative research) approach to identify risk factors, geographic patterns, and perceived barriers to care for diabetes and PAD-related amputation in WV. A cluster of high-risk zip codes were identified within the county, and research results were translated into accessible language and disseminated to key stakeholders in the community. Resulting community conversations led to a practice-based research project seeking to adapt evidence-based interventions for amputation prevention to local clinics. These interventions include adaptations of diabetic foot exams with risk stratification and decision-making, a multidisciplinary limb preservation team brought to rural clinics via telemedicine/Project ECHO, and an adaptation of the "hot-foot hotline" that enables primary care physicians to reach our vascular triage nurses directly in case of emergency.

What is unique about this project is the rigorous community engagement that has occurred at every level and works in tandem with the project. We have a project advisory board of primary care providers and amputation prevention specialists in the area who provide input on the intervention, and we also have a very active community advisory board that came together organically during the project development phase. This board has identified priorities for the community to prevent diabetes and vascular disease–related complications on a larger scale. For example, they created a diabetes resource guide for community members and a robust diabetes support group and have applied for federal funding for better access to healthy foods. By working at the community level, there is a level of motivation, engagement, and connection that helps propel all levels of the intervention. It also elevates the health of the community through multiple mechanisms and is transformational, as community-engaged research is meant to be. By motivating and empowering the community to take their health into their own hands, our project has a level of sustainability that will ensure a lasting impact well beyond our grant period.

What does the ideal comprehensive, multidisciplinary CLI/CLTI care team/program of the future look like?

Drs. Mena-Hurtado and Smolderen: Any type of integrated care that addresses the entire person and is proactive, evidence-based, and data-driven, with systems in place to deliver equitable, high-quality, and accountable care and has financial incentives toward delivering good outcomes. At the same time, further investment in training of integrated care models and quality standards for centers of excellence that can meet all the criteria of delivering high-quality CLI/CLTI care.

Dr. Portou: I have given this question a lot of

thought over recent years in my capacity as subspecialty lead for PAD in my institution. As I've mentioned, targeted interventions for reducing the progression to PAD and early cardiovascular disease–related death through overall health promotion, risk factor management, supervised exercise, and best medical therapy are absolute priorities, and they should be occurring alongside all other activities.

A thorough CLTI prevention program can be provided by clinical nurse specialists who will work closely alongside other vascular consultants and specialists. Part of their role would be community and primary care liaison and education, aiming to capture those early symptomatic individuals before it's too late. Close working relationships with cardiologists, diabetologists, and renal and other metabolic physicians to optimize coexisting comorbidities will also enable at-risk patients to be identified.

For established CLTI patients, early recognition and rapid referral to specialist units are essential and require rapid-access clinics staffed by vascular specialists with immediate access to diagnostics such as duplex. Vascular scientists are a fundamental part of this care team. Nurse specialists or physician associates ensure pathway navigation and care continuity. CLTI-specific multidisciplinary case meetings involving vascular specialists, interventional radiologists, and anesthetists discuss and determine consensus treatment approaches and enable suitable treatment times and locations (and personnel) to be assigned based on urgency, complexity, and skill set requirements. That is the vision.

Dr. Minc: Clinicians dedicated to treating CLTI must be able to work within a multidisciplinary, collaborative team with appreciation and respect for each other's area of expertise. Ideally, CLTI teams should include clinicians experienced in revascularization, wound care, complex reconstruction, infection control, endocrinology, and nutrition. Given the realities of CLTI care and the needs of communities struggling with high amputation rates, additional staff who can coordinate patient care and mobilize resources to empower patients to adhere to treatment plans are essential. These include clinic coordinators, patient navigators, and community health workers. Finally, research/quality coordinators are an invaluable asset to a CLTI team, as they can track and report outcome metrics and help patients access clinical trials when appropriate. ■

1. 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. Published online April 25, 2023. doi: 10.1016/S0140-6736(23)00462-2

2. Farber A, Menard MT, Conte MS, et al. Surgery or endovascular therapy for chronic limb-threatening ischemia. N Engl J Med. 2022;387:2305-2316. doi: 10.1056/NEJMoa2207899

Disclosures

Dr. Mena-Hurtado: Receives grant funding from Shockwave Medical; consultant to Abbott Laboratories, Cook Medical, Haemonetics, and Optum Labs, Inc.

Dr. Smolderen: Receives unrestricted research grants from Cardiva Medical Inc., Cook Medical, Merck & Co., Inc., Shockwave Medical, and Janssen Pharmaceutical Companies of Johnson & Johnson; consultant to Optum Labs, Inc., Happify, Haemonetics, and Abbott Laboratories.

Dr. Portou: None.

Dr. Minc: Receives grants from National Institute of Diabetes and Digestive and Kidney Diseases [K23DK128569] and the Society for Vascular Surgery Foundation/American College of Surgeons. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health, the Society for Vascular Surgery Foundation, or the American College of Surgeons.