PANEL DISCUSSION

The Evolving PAD Patient Population: How Is It Changing?

Recognition of generational trends and their impact on decision-making and patient care.

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Dr. Schneider: How do overall trends in life expectancy manifest in the peripheral artery disease (PAD) population, and how might they factor into decision-making? How does the decrease in mortality due to heart disease and cancer treatments affect your PAD practice?

Dr. Rogers: In a query from a nationwide database, PAD-related mortality actually decreased from 2000 to 2016 but then plateaued in 2016 to 2019.[1] Men, non-Hispanic Black or African American individuals, those aged ≥ 85 years, and those living in rural counties were the highest-risk subgroups. With better detection and therapies for competing diseases (cardiac disease, malignancies), there is more room for PAD patients to see improvements in limb-specific outcomes. More aggressive approaches to efficient limb salvage may benefit a PAD patient who has less risk of mortality due to myocardial infarction and stroke or malignancy.

In managing PAD patients, we can learn from disciplines like oncology and cardiology: identify pathology early, have a broad evidence base of clinical research in various subgroups, and provide specific therapies to reduce disease-specific outcomes.

Prof. Steiner: Life expectancy in Western countries has steadily increased over the past few decades, largely

due to advancements in health care and public health measures. Thus, preventive measures, improved pharmacotherapy, and invasive treatment options for cardiovascular diseases have advanced significantly, leading to improved prognosis for patients and longer survival. In parallel, enhanced screening, targeted therapies, immunotherapy, and advancements in radiation and surgical techniques have increased survival rates and improved quality of life in cancer patients. However, this progress has begun to plateau in several countries, primarily due to the rising incidence of lifestyle-related diseases (eg, obesity, diabetes).

As a result of the aging population and shifting demographic trends, the number of individuals diagnosed with PAD and requiring treatment is on the rise. In my daily practice, I have seen and treated an increasing number of patients with very complex disease and advanced comorbidities in recent years. However, disparities in life expectancy remain significant among different socioeconomic groups, with factors such as income, education, and access to health care playing crucial roles. The PAD population is particularly affected, as many patients come from socially disadvantaged backgrounds, and this must be taken into account in decision-making.

Lifestyle modification needs to be addressed, and comprehensive risk factor management is essential. The primary focus should be on increasing the number of years lived in good health, which can be achieved through targeted interventions and education. For patients undergoing endovascular interventions, particularly those with claudication, it is crucial to consider long-term outcomes not only addressing the immediate clinical needs but also the underlying factors and long-term prognosis of these interventions.

Dr. Beckman: PAD is not uncommonly diagnosed after a patient has a cardiac event. Improvements in therapy to minimize cardiovascular disease and the impact of cardiac events portend an ever-greater population of people newly diagnosed with PAD as a result of a vascular examination or more in-depth exam. Similarly, many of the risk factors for cancer are similar for PAD such that this population is at higher risk for PAD than a noncancer population. Finally, some recent cancer therapies impair vascular function and may advance atherosclerotic cardiovascular disease.

Dr. Schneider: The incidence of diabetes continues to rise. How is this trend affecting PAD patients and outcomes expectations?

Dr. Beckman: Diabetes increases the risk of developing PAD by two- to fourfold, enhances the risk of adverse limb events, and renders the outcomes of procedures and surgeries less effective. If diabetes fosters the development of microvascular disease, the risk of amputation is significantly increased.

Prof. Steiner: Diabetes is strongly associated with the development and progression of infrapopliteal disease. This results in an increasing number of diabetic patients requiring complex below-the-knee (BTK) interventions, often as part of a multilevel disease presentation. Although we can achieve acute procedural success with endovascular interventions in many patients, long-term outcomes remain challenging due to high rates of failure caused by issues such as recoil and neointimal hyperplasia. Currently, we have limited treatment options to address these complications. Additionally, lesion heterogeneity is especially pronounced in (diabetic) BTK disease, characterized by a variety of disease patterns that encompass different types of calcification (both intimal and medial), along with fibrotic and thrombotic components of occlusive disease. This complexity may necessitate different treatment approaches, and hopefully we can define tailored strategies more effectively in the future with support from dedicated clinical trials.

Dr. Rogers: Diabetes is a well-established risk factor for PAD, as well as atherosclerotic disease of other vascular beds. Up to 70% of patients with diabetes aged > 70 years have PAD.[2] Diabetes confers a higher risk of mortality, amputation, and severity of presentation (chronic limb-threatening ischemia [CLTI] vs claudication or asymptomatic).

The implications are multifold: First, we should take initiative in identifying PAD in patients with diabetes. Second, we should be aggressive in educating good foot hygiene, implementing secondary prevention measures, and establishing regular follow-up in patients with PAD and diabetes. Third, we should not attribute lower extremity tissue loss to diabetes alone without considering ischemia and presence of PAD. Fourth, to achieve optimal limb outcomes, we need to comprehensively address not only PAD and atherosclerotic disease but also glycemic management, diabetes, and any associated infection, wound care, or foot surgery—with the goal of efficiently preserving a functional limb.

Dr. Schneider: Similarly, what trends are you seeing in the rates of renal failure and its impact on PAD prevalence and outcomes?

Dr. Rogers: Chronic kidney disease (CKD) is also an established risk factor for PAD.[2] Studies often dichotomize those with and without CKD based on estimated glomerular filtration rate (eGFR) of varying cutoffs (eg, 60, 45, 30,

or 15 mL/min). Patients with even worse renal function who require renal replacement therapy are usually excluded from cardiovascular studies. In practice, the degree of renal dysfunction is a spectrum; whether it confers a completely linear spectrum of cardiovascular risk or whether there are certain cutoff points of eGFR, or other measures of risk, is not known. It is also not known whether CKD confers excess risk for all atherosclerotic disease states (eg, cerebrovascular, coronary, lower extremity) or rather contributes to risk of a specific vascular bed.

Despite these unknowns, CKD certainly seems to add to the complexity of treating PAD. There is a higher prevalence of PAD in the CKD population than the general population.[2] In my experience, CKD patients with PAD have more complex anatomy (calcification and BTK disease), making revascularization more challenging. There are also considerations in the CKD patient regarding administration of iodinated contrast, risk of contrast nephropathy, and worsening long-term renal function. Finally, medical therapy is more challenging in the CKD patient; one must consider the renal clearance of cardiovascular medications and/or effect on renal function, for example. In my opinion, the CKD population with PAD is a special PAD subgroup that is analogous to but distinct from diabetes.

Dr. Beckman: I don't see much renal failure in my practice, but I do see that CKD impacts outcomes significantly as well. It is a common downstream effect of diabetes.

Prof. Steiner: Renal failure has increasingly become a prevalent comorbidity. Patients with advanced CKD are at a higher risk of developing contrast-associated acute kidney injury during endovascular interventions, which has been linked to poorer acute and long-term outcomes, including increased mortality rates. When performing endovascular interventions, I typically use CO_2 angiography for renal protection in this population.

In my practice, I increasingly treat another unique and challenging patient population: individuals with end-stage renal disease (ESRD) who often present with advanced distal disease, including severe cases such as "desert foot." A notable characteristic is that these patients often remain clinically asymptomatic for an extended period, only to abruptly progress to CLTI, typically presenting with a circumferential sheath-like pattern of vessel calcification. These circumstances frequently lead to a situation where neither endovascular nor surgical options are viable. Although deep venous arterialization has emerged as a promising treatment option for these patients, it is crucial to develop strategies for early identification of individuals at risk. Doing so could ultimately help alter the course of the disease and improve patient outcomes.

An intriguing parallel exists between patients with ESRD and those with CLTI; neither population has benefited from the declines in mortality rates observed in other cardiovascular disease groups over the past few decades. This disparity underscores the severity of their conditions and emphasizes the urgent need for earlier intervention.

Dr. Schneider: Cigarette smoking, on the other hand, is decreasing. What might this mean both for PAD incidence and possible outcome trends?

Dr. Beckman: The current appreciated view of PAD is that cigarette smoking causes more proximal disease while diabetes causes more distal disease. I would anticipate a change in presentation, a more difficult landscape for revascularization, and more ancillary adverse effects of diabetes, such as neuropathy and microvascular disease, that potentiate PAD adverse outcomes.

Prof. Steiner: Smoking remains prevalent in my clinical practice, but individuals who quit and actively address other lifestyle and risk factors tend to achieve better outcomes. However, I do have significant concerns regarding a specific patient population: those presenting with premature PAD before the age of 50 or 55 years. The vast majority have complex lipid disorders and smoke, while a smaller proportion may have rare causes (eg, autoimmune diseases, HIV-related atherosclerosis). Both endovascular and surgical revascularization procedures exhibit extremely high failure rates, even with aggressive concurrent disease-modifying pharmacotherapy, highlighting that this represents a particularly aggressive form of PAD. We still do not fully understand all the pathophysiologic drivers involved, and I believe that further research is essential to determine the best treatment strategies for these patients.

Dr. Rogers: Smoking is a strong risk factor in PAD, both increasing the incidence of PAD and worsening limb and cardiovascular outcomes. Although a majority of patients who actively smoke tobacco products wish to quit, only a minority do. Despite trends in the prevalence of cigarette smoking worldwide, I think it is important not to deemphasize the significance of cigarette smoking on many health aspects but also PAD. Patients should be educated about the harms of smoking, and providers should be encouraged to prescribe pharmacologic and nonpharmacologic approaches for cessation, which are typically superior to self-directed cessation attempts alone.[2]

Dr. Schneider: How do you predict the new class of diabetes and weight loss drugs will affect the PAD population of the near future?

Dr. Rogers: Randomized trials of glucagon-like peptide-1 (GLP-1) agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors have demonstrated a reduction in major adverse cardiovascular events in those with cardiovascular disease, including PAD.[2] In that respect, these drug classes would be expected to contribute to improved survival of a PAD population. I think these medications have particular implications for patients with CLTI. Improved glycemic control should increase the ability to heal a wound and help prevent neuropathy, which often contributes to the development of tissue loss in those with diabetes. It will be interesting to have more data in PAD-specific diabetes populations that investigate the effect of these drug classes on limb-specific outcomes.

Prof. Steiner: New diabetes medications such as SGLT-2 inhibitors have shown survival benefits in various patient populations at high risk for cardiovascular mortality, including those with heart failure and CKD. Similarly, weight loss drugs have demonstrated cardiovascular protective effects, leading to the realistic hope that these benefits may also be applicable to PAD patients. My primary concern is how PAD patients will benefit from these advancements, given that undertreatment remains a significant issue in their care. Furthermore, there are currently no large dedicated clinical trials aimed at addressing this population, which would be instrumental in raising awareness. This is undoubtedly a critical issue for the vascular community.

Dr. Beckman: So far, these drugs have been incredible successes for cardiovascular and heart failure patients. I would surmise that limb benefits, particularly from GLP-1 receptor agonists, may have both functional benefits and reduce events like revascularization and amputation.

Dr. Schneider: In terms of PAD trends, the discussion has been that disease seems to be moving more distal in the vascular beds and below the ankle (BTA). What have you seen clinically? Has small-artery disease increased and pedal artery runoff diminished? And, what are the ramifications of these trends?

Dr. Rogers: I certainly think we are more *aware* of infrapopliteal and pedal disease. This perceived increased awareness likely stems from improved imaging techniques and advances in revascularization techniques. We surprisingly have a paucity of data correlating PAD anatomy with limb outcomes and clinical subgroups as well as the prevalence of certain anatomic patterns, such as distal disease. As this knowledge gap is addressed, we may find that BTK disease is an anatomic pattern associated with a CLTI phenotype. This has implications for diagnostic modalities, revascularization tools, and approaches for this clinical subgroup at high risk of limb loss.

Anecdotally in my practice, I find disease of the superficial femoral artery to be prevalent and isolated disease of the superficial femoral artery more likely to be associated with claudication rather than CLTI.

Dr. Beckman: In my impression, over recent years, we see more symptomatic disease with a distal presentation and more calcification in these vessels as well. Revascularization is more difficult in these settings as there may not be targets to fix.

Prof. Steiner: An increasing number of patients are presenting with distal BTA disease, particularly among those with diabetes and ESRD. We must acknowledge that distal embolization can be a concern during endovascular interventions, potentially impacting the pedal arteries as well. We also know that concomitant microcirculatory disease is associated with an increased risk of amputation in diabetic patients, highlighting the potential complications of subclinical microembolism. With further advancements in techniques and specialized devices, BTA interventions can be successfully performed. But, there is still limited evidence regarding optimal patient selection and long-term outcomes for these procedures.

Dr. Schneider: Are we seeing more calcification and more diffuse disease than in years past?

Dr. Rogers: Similar to the anatomic pattern of BTK disease, I think we are more *aware* of calcification, likely due to better imaging modalities and challenges encountered as revascularization techniques "push the envelope," so to speak. However, it is intuitive that we would also be seeing more calcification as populations age, the prevalence of diabetes increases, and patients with CKD live longer due to overall cardiovascular risk reduction. As advances in medical therapy (particularly lipid-lowering and new medical therapies for diabetes) become more widely adopted and have time to take effect on a population level, I would like to be optimistic that PAD will become less diffuse and more focal, which would simplify revascularization and perhaps lessen the severity of clinical presentation.

Dr. Schneider: How might these changes influence treatment of claudication? Of CLTI?

Dr. Rogers: Decreasing the active smoking rates and improving glycemic control in those with diabetes, as well as other risk factor modifications, should decrease the incidence of PAD and severity of clinical presentation

and improve outcomes after revascularization. Better understanding of anatomy and its association with outcomes in clinical subgroups, such as those with claudication or CLTI, will be insightful in clinical decision-making. Perhaps there is an anatomic phenotype (heavily calcified disease, long occlusions, certain anatomic levels) that is best managed conservatively in a patient with claudication or, if revascularized, necessitates aggressive medical therapy (antithrombotics) to achieve an optimal limb outcome. Another example related to CLTI might be to better understand the relationship of BTK anatomy to guide revascularization strategies for limb salvage (eg, does one revascularize all tibioperoneal arteries or choose one artery, and, which artery?). Many PAD practitioners have intuition regarding these issues based on experience; it will be beneficial to support this intuition, or revise it, with data.

Prof. Steiner: For patients with claudication, access to disease-modifying pharmacotherapies, support for lifestyle modifications (eg, smoking cessation, exercise training), and durable revascularization options that allow for potential future procedures within an individualized treatment approach are crucial to ensuring a good quality of life and maximizing the number of years lived in good health.

Patients with CLTI require a comprehensive and multidisciplinary treatment approach that is tailored to their overall health, comorbidities, ischemia severity, disease patterns, and personal preferences. The primary objectives are to relieve symptoms, enhance quality of life, preserve limb function, and prevent the progression of ischemia. There is an urgent need for strategies to identify patients at risk for CLTI and develop treatment algorithms aimed at altering disease progression whenever possible. ■

1. Issa R, Nazir S, Khan Minhas AM, et al. Demographic and regional trends of peripheral artery disease-related mortality in the United States, 2000 to 2019. Vasc Med. 2023;28:205–213. doi: 10.1177/1358863X221140151
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Disclosures
Dr. Schneider: Consultant to Silk Road Medical, Surmodics, Endologix, Healthcare Inroads, Cagent Vascular, Medtronic, Boston Scientific Corporation, Philips, and Acotec.
Dr. Beckman: Consultant to Novartis, Medtronic, JanOne, Mingsight, Tourmaline, and Merck.
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