Optimal Medical Therapy for CLI: Recent Advances and the Need for More Data

A conversation with the President of the Society for Vascular Medicine on current best practices for medical therapy in this challenging population.

WITH HEATHER L. GORNIK, MD

How would you summarize current capabilities for treating peripheral artery disease (PAD) with medication alone or combined with exercise?

From my perspective, the bottom line is that for most patients with PAD—and particularly for those with asymptomatic disease, stable claudication, or other leg symptoms—medical therapy with supervised exercise therapy (SET) will get you very far, so far that revascularization is generally not needed. Critical limb ischemia (CLI) is a different "animal" entirely, and revascularization in addition to medical therapy is necessary to save limbs.

Do you believe there is sufficient awareness regarding optimal medical therapy guidance in patients with PAD, both in primary and adjunctive settings?

What continually amazes me about PAD is that there are effective medical therapies to prevent cardiovascular events and improve function for all patients, but these therapies are woefully underprescribed and underutilized. Patients may have undergone lower extremity revascularization for stable claudication and superficial femoral artery stenting, but they are not on a statin! Capabilities to impact outcomes are there, but they are not deployed effectively. As the Editor-in-Chief of *Vascular Medicine*, I review multiple observational studies every year that describe the underprescription of medical therapies among patients with PAD in various settings. Let's stop describing the problem and instead find innovative ways to fix it—I'm ready for a new narrative.

What can be done to further establish awareness and ensure best practices?

One simple thing that can be done is for all vascular specialists to embrace a "the buck stops with me" attitude in terms of medical therapy for a patient with PAD. I've often heard from interventional and surgical colleagues who didn't want to put a patient on a statin or angiotensin-converting enzyme inhibitor or add rivaroxaban to aspirin because they didn't want to offend the referring physician. The bottom line is that this is happening for many of our patients who don't end up being prescribed recommended therapies by anyone; therefore, all vascular specialists should be the stewards of medical therapy for their patients with PAD.

How would you differentiate the effectiveness in treating claudication versus CLI?

Unfortunately, there are problems treating patients with PAD across the entire spectrum of disease. Patients with stable symptoms, such as walking impairment, are not diagnosed as having PAD, and at the other end of the spectrum, patients may undergo amputation without being assessed for PAD and limb perfusion. There remains a general lack of awareness and empowerment to recognize and treat PAD outside the vascular specialist, podiatry, and cardiology communities. Some headway has been made in the past

RECOMMENDED READING

1 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease

Executive summary: a report of the American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines

Gerhard-Herman MD, Gornik HL, Barrett C, et al. Circulation. 2017;135:e686–e725

Provides a primer on treating patients with PAD across the disease spectrum, including CLI.

2 The natural history of untreated severe or critical limb ischemia

Abu Dabrh AM, Steffen MW, Undavalli C, et al. J Vasc Surg. 2015;62:1642–1651.e3

Emphasizes the terrible outcomes among patients with CLI, including the high rate of amputation among those not revascularized.

3 The Society for Vascular Surgery lower extremity threatened limb classification system: risk stratification based on wound, ischemia, and foot infection (WIfI)

Mills JL Sr, Conte MS, Armstrong DG, et al. J Vasc Surg. 2014;59:220–234.e2

Outlines a new standard in terms of how clinicians communicate about CLI.

4 Validation of the relationship between ankle-brachial and toe-brachial indices and infragenicular arterial patency in critical limb ischemia

Bunte MC, Jacob J, Nudelman B, Shishehbor MH. Vasc Med. 2015;20:23–29

Demonstrates the great disconnect between ankle-brachial index and disease severity among patients with CLI.

5 Association of statin dose with amputation and survival in patients with peripheral artery disease

Arya S, Khakharia A, Binney ZO, et al. Circulation. 2018;137:1435–1446

Looks at the effect of statin use and intensity on patients with PAD (almost 30% of patients with PAD in this series were not on a statin; statin use prevented death and amputation, and high-intensity statin was associated with greatest benefit in outcome).

decade, but there is still such a long way to go in educating the medical community at large about this disease and how to manage it. That includes educating general practitioners, internists, and advanced practice providers.

Where do we most need new data? Which ongoing trials do you believe will yield the most relevant data for current practices?

I am excited about recent trials that focused on determining optimal antiplatelet/antithrombotic strategies for patients with PAD. Although there are many unanswered questions, the COMPASS trial[1] was an important study that enrolled patients with stable atherosclerotic disease, including PAD, and found a benefit of low-dose rivaroxaban (2.5 mg twice daily) plus aspirin compared with aspirin alone in terms of cardiovascular and limb outcomes. This was a landmark study because previous studies have not shown a benefit of anticoagulation (ie, warfarin) in patients with PAD, and COMPASS showed a benefit with this regimen in terms of preventing both cardiovascular and limb outcomes. VOYAGER PAD (NCT02504216), the companion trial to COMPASS, is focusing on optimal therapies after lower extremity revascularization and will include patients with CLI. I am particularly excited about those data.

The other medical therapy "stories" I have been following with interest are the trials of novel therapies to treat diabetes, such as the sodium glucose cotransporter-2 and glucagon-like peptide-1 inhibitors and their potential for impact on cardiovascular and perhaps limb outcomes among diabetic patients. I'd also love to see more data on PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors among patients with PAD across the spectrum of disease.

What are the hallmarks of an effective SET program? What are the keys to maintaining compliance in patients with lower extremity pain and compromised function?

The coverage determination for SET published by the Centers for Medicare & Medicaid Services has a nice description of an optimal SET program for PAD.[2] The walking-focused sessions involve the patient intermittently walking to moderate-to-severe pain, resting, and then walking again. Sessions are supervised and occur longitudinally (the Medicare coverage benefit includes 36 sessions over a 12-week period with potential for a second 12-week program). SET for PAD is sometimes a tough sell for our patients because, by definition, showing up and participating means that they will experience some pain. Because of this, it is particularly important for the staff to coach and encourage patients and remind them to focus on what we know to be potentially very positive outcomes in terms of walking function and quality of life if they can stick with it. To be honest, the copays are also a barrier for some patients. At my institution, the PAD SET program is incorporated into the cardiac rehabilitation program, and that model seems to work well.

Do you know of any app-based or wearable technologies that assist with either medical or exercise therapy compliance for PAD?

There's been some nice work done in this space by Dr. Mary McDermott with Northwestern University and Dr. Andrew Gardner with Penn State College of Medicine involving semisupervised or home-based programs using accelerometer or Fitbit (Fitbit, Inc.) devices. These have shown some modest successes but not to the extent of supervised programs. It seems the coaching and direct supervised encouragement during exercise are important.

You recently became Co-Director of the Vascular Center at University Hospitals Harrington Heart & Vascular Institute. What are some of your initial goals with respect to its PAD and CLI program?

First of all, I was attracted to the position because it gave me the opportunity to partner with two terrific colleagues and friends—vascular surgeon Dr. Vikram Kashyap and endovascular specialist Dr. Mehdi Shishehbor—in growth of a truly integrated, multispecialty vascular service line. Our mission is to deliver the best vascular care possible throughout Northeast Ohio across a large, diverse health care system that includes a traditional urban academic medical center, smaller community hospitals, and even rural facilities. My focus thus far has been on expanding our noninvasive vascular care footprint and growing our team of noninvasive vascular medicine providers who can serve as gatekeepers to advanced vascular care in the health care system. I've been impressed by the cutting-edge interventional therapies for CLI being performed here, and I'm looking forward to seeing the outcomes of a limb salvage advisory council program Dr. Shishehbor started (analogous to a tumor board for oncology) with the goal of significantly reducing/preventing amputations system-wide. Finally, one of my junior partners, Dr. Khendi White Solaru, is a vascular medicine specialist who is focused on community-based interventions to tackle health disparities in PAD outcomes in Cleveland, and I've really enjoyed working with her on this.

If you could have five publications be required reading for all physicians treating CLI, what would they be?

A few classics are listed in the *Recommended Reading* sidebar, with the caveat that they are biased toward diagnostics and medical therapies—there are many classical endovascular and surgical publications too. In reference to the article by Arya et al, I think all patients who undergo a vascular procedure should be sent home on a statin, ideally at high-intensity dosing. ■

1. Anand SS, Bosch J, Eikelboom JW, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet. 2018;391:219-229.
2. Centers for Medicare & Medicaid Services. Decision memo for supervised exercise therapy (SET) for symptomatic peripheral artery disease (PAD) (CAG-00449N). https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=287. Accessed May 2, 2019.

Heather L. Gornik, MD
Co-Director, Vascular Center
University Hospitals Harrington Heart & Vascular Institute
Cleveland, Ohio
President, Society for Vascular Medicine
Editor-in-Chief, *Vascular Medicine*
heather.gornik@uhhospitals.org
Disclosures: Ownership/equity related to FlexLife Health, Inc.