CardioVascular Learning Network

PAD Patient Pathways:

CONSENSUS GUIDELINES

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PAD Patient Pathways: Consensus Guidelines

INTENDED LEARNER

This initiative is intended for clinicians who encounter and care for patients who have or are at risk of developing PAD, including primary care physicians, NPs, PAs, interventional cardiologists, interventional radiologists, vascular surgeons, wound care specialists, podiatrists, pharmacists, nurses, cath lab technicians, and vascular technologists.

LEARNING OBJECTIVES

After participating in this activity, learners should be better able to:

- Describe recommended assessment and testing strategies for the diagnosis of PAD
- Employ patient-centered care strategies to reduce the risk of MACE and MALE in patients with PAD
- Assess the most current PAD guidelines for relevant clinical disciplines
- Evaluate patient pathways by specialty

CLAIMING CREDIT

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Release Date: September 1, 2023

Expiration Date: September 1, 2024

Estimated time to complete: 1 hour

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COMMERCIAL SUPPORT

Supported by an independent educational grant from Janssen Pharmaceuticals, Inc., administered by Janssen Scientific Affairs, LLC.

Overview

The goal of this educational article is to help readers identify best practices for the testing, diagnosis, management, and referral of patients with peripheral artery disease (PAD). Guideline recommendations for PAD management will be examined. In addition, experts from a variety of sites discuss their patient-centered care strategies to reduce the risk of major adverse limb events (MALE) and major adverse cardiovascular events (MACE). This activity is designed to enhance the use of evidence-based medicine, promote multidisciplinary care, and improve patient quality of life (QoL) and outcomes.

PAD is underdiagnosed, reflecting patient and provider factors. Symptomatic patients may dismiss their symptoms or attribute fatigue, cramping, and difficulty walking to age.[1] Providers, too, may attribute symptoms to age or another condition (such as spinal stenosis or arthritis), as only 10% to 30% of patients experience typical symptoms of intermittent claudication (IC). Some clinicians underappreciate the long-term health risks associated with PAD.[2]

A recent analysis calculated PAD prevalence at 21 million to 26 million in 2020.[3] There is a higher prevalence of PAD among individuals who are Black compared to those who are White. Critical limb ischemia (CLI), defined as PAD with resting pain, tissue loss, or nonhealing wounds, affects about 11% of patients aged > 40 years diagnosed with PAD.[2]

PAD is associated with a host of adverse outcomes. Ankle brachial index (ABI) < 0.90 has been found to triple all-cause mortality risk for both men and women compared to those with ABI of 1.11 to 1.40. It also increases the risk of coronary artery disease (CAD) by 45% and stroke by 35%.[4] The cumulative incidence of mortality for patients with CLI is about 20%, which is also the rate for amputation.[2] An analysis of Medicare claims found that 54% of patients had died within 4 years of the initial diagnosis of CLI.[5] PAD-related limb loss confers a severe prognosis. One-year mortality for patients who have a lower limb amputation is 48%.[4]

Risk factors for PAD include: age > 65 years; age of 50 to 64 years with atherosclerosis risk factors (diabetes, uncontrolled hypertension, dyslipidemia, or history of smoking); age of 50 to 64 years with a family history of PAD; and age < 50 years with diabetes and an additional risk factor for atherosclerosis. Chronic kidney disease (CKD), Black ethnicity, a sedentary lifestyle, and low socioeconomic status are also risk factors for PAD.[2, 6, 7]

Guidelines from the American Heart Association/American College of Cardiology (AHA/ACC) recommend that all patients with an increased risk for PAD undergo a comprehensive assessment of legs and feet.[7] Women are more likely than men to have atypical symptoms. Atypical symptoms can include pain in the hips, buttocks, or lower pain that occurs while walking and resolves at rest. Discomfort or weakness in the lower extremities are also atypical symptoms of PAD.[2] Patients with symptoms and/or examination suggestive of PAD should have a resting ABI test.[7] ABI can be abnormally high in some individuals, eg, those with diabetes or CKD, because of stiffened arteries which cannot be compressed. For these patients, measurement of the toe brachial index (TBI) may be useful. A TBI < 0.70 establishes a diagnosis of PAD.[7]

The AHA/ACC guidelines, which were issued in 2016, recommend antiplatelet monotherapy to reduce the risk of myocardial infarction (MI), stroke, and vascular death in patients with PAD. All patients with PAD should be placed on lipid-lowering therapy, and patients who smoke should receive smoking cessation counseling. Patients with elevated blood pressure or plasma glucose should be placed on appropriate therapy. Supervised exercise is recommended to reduce leg symptoms and improve functional status.[7, 8]

Dual pathway inhibition—targeting both platelets and thrombin— was developed as a strategy to reduce the risk of atherothrombotic events.[9] Since the release of the AHA/ACC guidelines for PAD, two randomized controlled trials (RCTs) demonstrated the effectiveness of a dual pathway inhibition strategy: COMPASS and VOYAGER PAD. COMPASS enrolled patients with PAD who were randomized to 2.5 mg rivaroxaban twice daily plus 100 mg aspirin, 5.0 mg rivaroxaban twice daily, or 100 mg aspirin only. The primary outcome was cardiovascular (CV) death, MI, or stroke. Dual inhibition significantly reduced the primary outcome, with a hazard ratio (HR) of 0.72 favoring rivaroxaban plus aspirin over aspirin monotherapy (P=0.0047). Rivaroxaban monotherapy did not significantly lower primary outcome events compared to aspirin. Both rivaroxaban treatment groups experienced more major bleeding than aspirin; however, there were no between-group differences for fatal bleeding or intracranial hemorrhage.[10] A prespecified analysis of the COMPASS trial showed that higher-risk individuals experienced a greater net clinical benefit from dual inhibition driven by a reduction in stroke and CV death.[11]

The primary PAD outcome of COMPASS was MALE, which was defined as severe leg ischemia requiring intervention or amputation. Dual inhibition significantly reduced the occurrence of MALE compared to aspirin monotherapy (HR of 0.54; P=0.0054), but rivaroxaban monotherapy did not.[10] Rivaroxaban plus aspirin lowered MALE by 43%, amputations by 58%, and peripheral vascular interventions (PVIs) by 24% compared to aspirin monotherapy. The investigators found that MALE was associated with an increased risk of subsequent hospitalization, amputation, all-cause mortality, CV death, MI, or stroke.[12, 11]

The VOYAGER PAD clinical trial enrolled patients with PAD who underwent surgical or endovascular revascularization. Post-procedure, patients were randomized to either dual inhibition with 2.5 mg rivaroxaban twice daily plus 100 mg aspirin once daily or placebo plus 100 mg aspirin. The primary efficacy outcome was a composite consisting of acute limb ischemia (ALI), vascular-related major amputation, MI, ischemic stroke, or CV-related death at 3 years. Dual inhibition was associated with significantly fewer primary efficacy events than aspirin monotherapy and lowered the relative risk by 15%. In particular, patients taking low-dose rivaroxaban plus aspirin were less likely to have an ALI compared to those taking aspirin alone (HR of 0.67). Major bleeding based on thrombolysis in myocardial infarction (TIMI) score was similar between the treatment groups. Rates of fatal bleeding or intracranial hemorrhage were similar between the two groups.[13]

Global vascular guidelines for the management of CLI, which were released in 2019, include similar medical therapy recommendations as those in the 2016 AHA/ACC guidelines for PAD. In addition, the global vascular guidelines include a recommendation for low-dose rivaroxaban plus aspirin in patients with CLI to reduced MACE and lower extremity ischemia.[6]

A multidisciplinary team is needed to optimize outcomes for patients with CLI, as no specialty can adequately address all the needs to lower limb-related morbidity and complications.[14] Team members include

endovascular interventionists, vascular surgeons, podiatrists, orthopedic surgeons, endocrinologists, nurses, wound care specialists, exercise physiologists, radiology and imaging specialists, and occupational and physical therapists, among others.[7] Without a multidisciplinary approach, care can be fragmented, and outcomes may suffer. Centers of Excellence for PAD are likely to have established care pathways. In other facilities, partnerships among specialties, eg, vascular surgery and/or endovascular intervention, podiatry, and wound care, have been developed to enhance the likelihood patients will see the appropriate specialist at the appropriate time.[14] Multidisciplinary teams have been shown to nearly double the length of time for amputation-free survival compared to standard wound care (P=0.02).[15]

Below, experts from different specialties at four facilities describe their practices for screening, diagnosis, and treatment of PAD.

Karen Bauer, DNP, APRN-CNP, CWS
Director of Wound Services
Program Director of UTMC Wound and HBO Center
UT Medical Center
Toledo, Ohio

Please describe your current PAD practice (caseload, practice setting, etc.).

I practice in numerous settings: acute care, ambulatory centers, and post-acute care. I am in a small metropolitan academic medical center as well as a rural critical access hospital and, thus, work with a broad range of vulnerable PAD patient populations. I see 20-30 patients a day, about half of which are wound patients—either chronic limb-threatening ischemia (CLTI) patients or other wound-related diagnoses, often with concurrent PAD. Our practice settings are unique, as our wound and vascular services are the same. Our advanced practice providers (APPs) are cross-trained in wound management and vascular surgery, and we have a vascular surgeon champion who embraces our PAD/CLTI patients. Because of our reputation in the area, more than half of the patients we see are PAD/CLTI patients.

Are you currently referring patients out or receiving referrals from other clinicians for PAD patients? Describe the pathway of the PAD patient in your experience.

We receive referrals for PAD patients from both within our systems and outside of them. Although we are a small center, we get referrals and see patients from a relatively large geographic area (40-70 miles) because of our rural practice site and our reputation. Our referrals come in a variety of ways. At times they are called directly to the MD or APP. Other time, referrals come through EPIC (our facility's EHR software system) or are called into our clinics or office. We have care navigator licensed practical nurses (LPNs) that help us track our patients.

Our wound care centers often serve as a gateway for our PAD patients. Sadly, patients oftentimes see their leg symptoms as a normal consequence of aging or as nonurgent, and, thus, don't come in early. We frequently see patients in the wound care centers as their first point of contact with a medical provider who self-refer because of skin discoloration or nonhealing wounds.

We also work closely with our orthopedic, rheumatologic, cardiothoracic, and family care providers. Because we are a small academic institution, we know and often see our referring providers. This makes care continuity and referral easier.

We do free screenings as well. In our metropolitan area, we advertise on social media and have patients call for screening appointments that are then done at our suburban office. In our rural setting, we take our ultrasound machine and do roundtable PAD education to community members and businesses. We then do screenings to follow. This generates referrals and improves access, too!

Please describe your current process for diagnosing and screening for PAD.

Our wound service is under the Division of Vascular, Endovascular, and Wound Surgery. Our diagnostic and screening process varies. Oftentimes, the wound care center is the gateway to vascular care, ie, the patient doesn't notice or know to come in for lower extremity symptoms until they have tissue loss (gangrene, distal ulcers, discoloration).

Unfortunately, we lack systematic protocols for PAD screening and diagnosis, but our MDs and APPs are diligent about recognizing PAD risk factors. We stress the importance of taking a thorough history and allowing the patient to feel comfortable sharing their experience with us. The prevalence of polyvascular disease is high; we are trained to recognize PAD symptoms in patients who are referred or present with other vascular symptoms (carotid, mesenteric, aortic, renal, etc.).

Our diagnostic tools vary by symptoms and physical exam, but generally involve ABI/pulse volume recording (PVR), arterial duplex, and/or computed tomography angiography (CTA). Because the majority of patients that present to us are symptomatic, we do not often check single-level or in-office ABI.

Why is screening so crucial?

Many PAD patients are asymptomatic, and amputation rates are high, especially in marginalized communities. It is up to us as providers to recognize risk factors and early symptoms to employ evidence-based, goal-directed medical therapy (GDMT) and risk factor modification to slow disease progression and prevent disabling symptoms and amputation. Recognizing PAD early through screening mechanisms also allows time for important lifestyle modifications, exercise therapy, and smoking cessation efforts that contribute to improved outcomes.

Are you working with a multidisciplinary team for the treatment of your PAD patients? If so, describe how that has improved patient care.

Yes. However, we lack many resources in our settings, eg, financial, supply, workforce, technology, so our systems are not optimally standardized or efficient. We make up for this with our commitment to patient-centered care. We don't have the ability to have formal care conferences or PAD/limb salvage programs, but we often have joint visits with our cardiology/rheumatology/orthopedic colleagues for team-based care. (Figure 1) Our physical therapy and cardiac rehabilitation departments are currently underutilized, but we are looking to optimize this.

In addition to interventions, are your putting your PAD patients on a medical therapy regimen to prevent MALE?

Yes! Again, while we lack resources, we remain diligent about evidence-based GDMT. Our APPs are crucial agents in ensuring adherence to medical therapy. The majority of our patients with diabetes are on statin and aspirin therapy, and we work closely with endocrinology/cardiology/primary care provider (PCP) for glycemic control and management of hypertension and hyperlipidemia. Our symptomatic PAD patients are also generally on a statin and antiplatelet

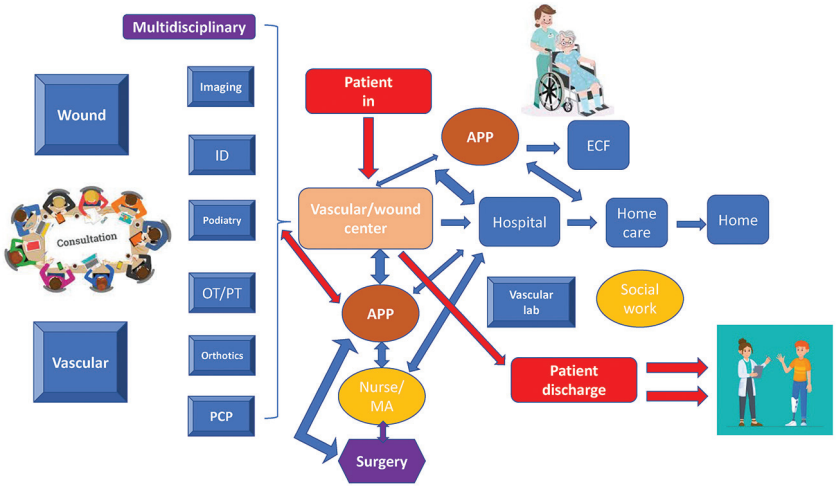

Figure 1. A Team-Based Care Approach to PAD

ID = infectious disease; OT = occupational therapy; PT = physical therapy; PCP = primary care provider; MA = medical assistant; ECF = extended care facility.

therapy. Smoking cessation is a routine part of our visits.

How has data from trials such as COMPASS and VOYAGER PAD changed your practice?

These studies have changed our practice significantly. As a result of them, we are not only more apt to consider and utilize dual-pathway inhibition, but also collaborating more closely with our cardiology colleagues to ensure same-page considerations when treating our CAD/PAD patients. Our practice is heavily CLTI weighted. Most of our patients have undergone repeat revascularization, either endovascular, hybrid, open, or a combination of all. Again, our APPs practice in all settings and thus see our patients across the continuum, which helps us streamline and monitor our patients on anticoagulation and antiplatelet therapy as well as to monitor bleeding.

What new technology or information excites you the most about the future of PAD treatment, and what will best optimize patient care?

Because I work so closely with so many underserved populations, I am most excited about the technologies that improve access to care, including screening mechanisms that can be performed outside of a healthcare setting. I am similarly excited about at-home monitoring. While these tools may not be diagnostic, they allow triage and recognition of a need for further care and provide the patient with a reference/objective data to encourage follow-through. While diagnostic and therapeutic technologies are exciting in the management of PAD/CLTI, our devices can only improve outcomes on patients that have access to them.

Anahita Dua, MBCHB, MBA, MSC
Director, Vascular Lab
Massachusetts General Hospital
Boston, Massachusetts
University of Colorado School of Medicine
Aurora, Colorado

Please describe your current PAD practice (caseload, practice setting, etc.).

I am an academic vascular surgeon at the Massachusetts General Hospital/Harvard Medical School. Approximately 70% of my practice is complex PAD.

Are you currently referring patients out or receiving referrals from other clinicians for PAD patients? Describe the pathway of the PAD patient in your experience.

At the MGH we offer endovascular and open limb salvage services to patients with PAD. Our services range from a dedicated supervised exercise therapy program for PAD all the way through to deep venous arterialization for the no-option patient facing amputation. I am the director of the Limb Evaluation and Amputation Prevention Program (LEAPP) at the MGH, which is a formalized, multidisciplinary program that includes vascular surgery, vascular medicine, plastics surgery, orthotics, vascular lab, interventional cardiology, interventional radiology, podiatry, wound care, infectious disease, and supervised therapy. Patients who present to the MGH are seen by our vascular nurse practitioner (NP) who then obtains initial screening imaging and appointments in a timely fashion with all the services the patient needs to see to optimize limb outcomes.

Please describe your current process for diagnosing and screening for PAD.

All patients are seen initially by a clinician, and ABIs and toe pressures are obtained. A diagnosis of PAD is made based on this imaging in conjunction with the clinical history and examination (rest pain, intermittent claudication, nonhealing wounds).

Why is screening so crucial?

Screening for PAD is absolutely crucial as a number of these patients, especially those who are smokers and/or have diabetes, may have associated neuropathy and may not present with classic signs of pain. We aim to catch patients before they present with nonhealing wounds so that they may be optimized to not only reduce their PAD morbidity but also morbidity associated with correlated vascular beds, including MI and stroke.

Are you working with a multidisciplinary team for the treatment of your PAD patients? If so, describe how that has improved patient care.

As mentioned above, we have a state-of-the-art limb salvage center at the MGH, which includes active participation from every discipline associated with limb care. This means 1) we have buy-in from all specialties that these patients have to be seen promptly and managed; 2) we are on the same page as to what the current best standard of care is for a PAD patient; and 3) we can follow up on outcomes to ensure that we are decreasing amputation rates and increasing wound healing to allow patients to be as functional as possible.

In addition to interventions, are your putting your PAD patients on a medical therapy regimen to prevent MALE?

Absolutely! The procedure to restore blood flow is very much a part of the story. Maintaining that blood flow is crucial as it takes on average 200 days for a diabetic wound

to heal. Antiplatelets and anticoagulants are key to this in conjunction with statin therapy and hypertensive therapy to ensure that mortality rates from stroke and MI are also reduced in this vulnerable population.

How has data from trials such as COMPASS and VOYAGER PAD changed your practice?

I do prescribe 2.5 mg rivaroxaban twice daily on a regular basis based on the trial data.

What new technology or information excites you the most about the future of PAD treatment, and what will best optimize patient care?

I am excited to see what transcatheter deep venous arterialization will do for the patients who have no option except amputations.

John N. Evans, DPM
Chief of Podiatry, Beaumont Hospital
Dearborn, Michigan
Private Practice
Allen Park, Michigan

Please describe your current PAD practice (caseload, practice setting, etc.).

I have an office-based private practice in a suburban community in southeast Michigan. I usually see between 25 and 30 patients daily (of all ages) for general foot and ankle concerns. Most of my patients are over 55 years old, and about 60% have diabetes. Within this population I see a significant amount of cardiovascular disease, with the additional risk factors of hypertension, smoking, dyslipidemia, diabetes, and chronic kidney disease being quite common. Often these patients will have had previous cardiovascular events, such as heart attack or stroke. With so many common risk factors within this group, I am continuously on the lookout for PAD.

Are you currently referring patients out or receiving referrals from other clinicians for PAD patients? Describe the pathway of the PAD patient in your experience.

I have a very active referral pattern for patients who I feel are likely to have PAD. I work with a number of vascular specialists to whom I refer patients for evaluation and treatment of PAD. I also involve the patient's primary physician along with various specialties, including cardiology, interventional radiology, endocrinology, and nephrology based on the individual's comorbidities. Many of my referring physicians are aware of my interest in diabetes and PAD and will send their patients to me for evaluation and long-term monitoring of their feet and legs, especially if they have a history of wounds or ischemic changes.

Please describe your current process for diagnosing and screening for PAD.

With all my patients I begin with an interview regarding their medical history and present symptoms. Those who have a history of atherosclerotic disease undergo a more thorough questioning, since these people are already at a higher risk of PAD. Are they active? Do they smoke or use other forms of nicotine? Are they able to walk one or two blocks without a problem? Are they able to climb stairs comfortably? Do they participate in activities that require some degree of exertion, such as gardening, golf, bowling, or shopping?

Next, the medical history is investigated. I start by reviewing the medications they are presently taking. It is common to meet someone who is on medication to reduce blood pressure, lipids, and hyperglycemia, and may have a history of MI, transient ischemic attack (TIA), or stroke. With this patient group, especially if they are over 60 years of age, I presume they are at risk for PAD until it is otherwise ruled out.

I recommend all podiatrists have the means to evaluate their patients for PAD utilizing in-office non-invasive vascular testing. Over my career, I have used technology performed in-office with my staff and have also contracted with a vascular diagnostic company to perform in-office testing. Each has its benefits, and one may fit better into the practice protocol than the other. At times I will refer the initial testing to imaging centers, or if they have a cardiologist I will ask them to perform the exam. The goal is to obtain a baseline study of the vascular supply ideally before any symptoms develop. Based on the findings of my examination and the vascular testing, the decision will be made whether the patient needs to see a vascular specialist or if we continue to monitor progress in the office setting.

More recently, technology has become available that can measure the oxygenation of the tissue within the dermis directly. This is especially useful in patients who have wounds or when determining if there is adequate tissue oxygenation for surgery to heal, or, if an amputation is needed, at what level would the limb most likely heal. Historically this has been difficult to determine because we had no simple way of measuring microcirculation, an often-overlooked aspect of the vascular system. Utilizing the technology of spatial frequency domain imaging or near-infrared spectroscopy, tissue and hemoglobin levels can be measured and quantified at the level of the dermis in the clinical setting. This is a useful adjunct to standard vascular testing, which focuses on the macrocirculation involving the larger arteries.

Why is screening so crucial?

Screening patients for PAD is crucial for a number of reasons. First, the majority of PAD patients are asymptomatic. When they do have symptoms, they are often atypical, and are told they have arthritis or are "just getting old." Once a person reaches a level of ischemia where they have claudication pain or have developed a nonhealing wound or gangrene, the process has reached an advanced stage that may require an intervention. The development process of atherosclerosis can begin early in life, sometimes in the patient's teenage years. It is a progressive problem that will continue throughout their life. When a symptom of ischemia develops, they are well down the path of PAD. The earlier we can diagnose the process, the better the result for the patient in the long term.

Next, PAD has poor "PR." Recent estimates of PAD have determined that up to 26 million Americans are afflicted with this disease.[3] For such a common problem, the public is often unaware of the frequency of the disease or its morbidity and mortality. CLI, an advanced stage of PAD, has a five-year mortality rate, higher than most cancers.[5] And research has shown that up to 30% of physicians are unaware that their patient has PAD.[16] Until the person reaches the level of ischemia where tissue loss has occurred or claudication symptoms are present, the diagnosis is not established, and the progression of this problem continues. When the same person has heart disease, hypertension, or diabetes, they are treated as early in the disease process as possible. But with PAD, treatment rarely begins until symptoms develop. For these and other well-documented reasons, screening for PAD is extremely important.

Are you working with a multidisciplinary team for the treatment of your PAD patients? If so, describe

how that has improved patient care.

I am not involved in a formal multidisciplinary team, but within my practice, I have developed networks where my patient can receive specialty vascular care, including intervention if needed, along with involvement with other recognized specialist team members (vascular medicine, rehabilitation, internal medicine, nutrition, social work, etc.) who are key for the success of patient care. There are a few formal multidisciplinary teams in my geographic area, most notably the University of Michigan, being one of the most successful in both patient care and research. Multiple studies have shown that formal multidisciplinary CLTI teams provide the greatest potential for limb preservation, and the development of these programs should be a primary focus within our healthcare system.[14, 15, 17]

One important point is that podiatry should be a member of every PAD team. Whether dealing with wound care, surgical intervention, evaluating the biomechanics of the patient's foot structure and gait, providing at-risk foot care, and long-term monitoring of their vascular status before and after any intervention, the podiatrist is most appropriately suited to provide the greatest hope for better quality of life and limb preservation during the person's lifetime, as PAD is never "fixed."

In addition to interventions, are your putting your PAD patients on a medical therapy regimen to prevent MALE?

I feel strongly that GDMT be utilized in patients with PAD. I find it is common for these people to have deficits within the GDMT recommendations. This would include smoking cessation, hypertension control, moderate- to high-intensity lipid management, and glycemic control if indicated. Exercise is often overlooked, even though it has been shown to be a powerful factor affecting both the development and treatment of the atherosclerotic process. Structured exercise therapy should be considered as a primary intervention for all PAD patients. I feel it is important to take time to discuss the importance of these options that are directed at modifiable risk factors with my patients (and their families) and make a point to discuss my concerns with their primary physicians on a regular basis.

Most of the guidelines are based on research involving the heart and reducing MACE. A significant portion of the PAD population will have additional atherosclerotic disease, what we consider polyvascular disease, so following these guidelines is a good idea. But research has shown that PAD has some important differences from coronary or cerebrovascular disease. One finding is that PAD can affect different arteries differently. When histologic evaluation was done on above-the-knee versus below-the-knee amputations, the proximal vessel damage was similar to coronary disease, with greater atherosclerotic plaque and medial calcifications, whereas below-knee arterial disease showed a majority of atherothrombotic disease with chronic thrombotic occlusions within these vessels.[8] Research has shown avoiding MALE is extremely important not only in the short term but for the rest of the person's life. Experiencing a MALE will increase the risk of amputation up to 200 times with a three-times increased risk of death.[12] In other words, MALE is a bad thing to have and should be avoided if possible.

Consideration of the effect of thrombin on the pathogenesis of PAD has become a major area of research, and dual pathway therapy with both antiplatelet and anticoagulant therapy (utilizing low-dose aspirin and the factor 10a inhibitor rivaroxaban in a low dose) has shown to reduce MACE and MALE in both stable atherosclerotic patients and after lower extremity intervention.[10, 12] Single- or dual-agent antiplatelet therapy has been shown to reduce MACE, but their effect on PAD has not been as robust.[6, 7]

How has data from trials such as COMPASS and VOYAGER PAD changed your practice?

COMPASS and VOYAGER PAD studies provided important information about PAD and new effective treatment options. COMPASS was a large-scale (27,395 patients) global medical study of patients with stable cardiovascular disease.[18] VOYAGER PAD involved 6,564 patients, also from around the world, who had symptomatic lower extremity PAD and had undergone a recent peripheral intervention.[13] (Figure 2) Prior to their publication, the primary pharmacologic therapy for atherosclerosis was platelet inhibition, and a number of drugs have been developed to inhibit the platelet through different mechanisms. This therapy is quite successful in reducing MACE and has reduced mortality and improved the quality of life for these patients. But these drugs had no real effect on thrombin, a factor critical in the pathogenesis of atherosclerosis, and antiplatelet therapy alone did not seem to give the successful results in the legs as it did in the heart.

Thrombin and platelets are important factors in the clotting of blood and are essential to our survival. But they are also key agents in the development of atherosclerotic plaque leading to PAD, CAD, and cerebrovascular disease. Thrombin levels increase after a cardiovascular event for at least two years,[19, 20] and high peak thrombin levels have been associated with a three-times increase in the risk of cardiovascular death. As research has shown, atherothrombotic disease is prevalent in the leg, especially below the knee. In COMPASS, the combination of low-dose aspirin daily with the anticoagulant rivaroxaban 2.5 mg twice daily was shown to reduce MACE (by 24%) and MALE (by 46%) in stable atherosclerotic patients when compared to control, including a reduction in major amputation by 67%.[10, 12] VOYAGER PAD looked at patients who had undergone a recent intervention and found a 15% reduction in MACE+MALE, and a 33% reduction in acute limb ischemic events when compared to control (aspirin with or without clopidogrel).[13] In both studies, the safety trade-off was increased bleeding events in COMPASS (1.6 vs 1.9% control)[12] and VOYAGER PAD (2.7 vs 1.9% control).[13]

What new technology or information excites you the most about the future of PAD treatment, and what will best optimize patient care?

There are several exciting advancements in the understanding and treatment of PAD. Medical therapy advances in the treatment of diabetes are providing new options for controlling this disease, and research into metabolic syndrome and insulin resistance is helping to define its effect on atherosclerotic development. We now have multiple therapies to reduce lipid levels, and we better understand the importance of apoliproprotein B (apo B) in the disease process, along with drugs affecting the low-density lipoprotein (LDL) receptors and cholesterol metabolism by different pathways in the liver.

We have in-office technology to measure oxygen and hemoglobin levels within the dermis, which is useful to evaluate the microcirculation of our patients. These non-invasive, non-contact devices use near-infrared and visible light by way of spectroscopy and spatial frequency domain imaging that aid in

wound healing and surgical planning, giving clinicians valuable vascular information otherwise unavailable.

For patients who have advanced PAD and have been considered "no-option" for intervention, procedures utilizing venous arterialization are being used, where a vein is used as a conduit for blood into the foot and show "PROMISE" in reducing the requirement for amputation.[21]

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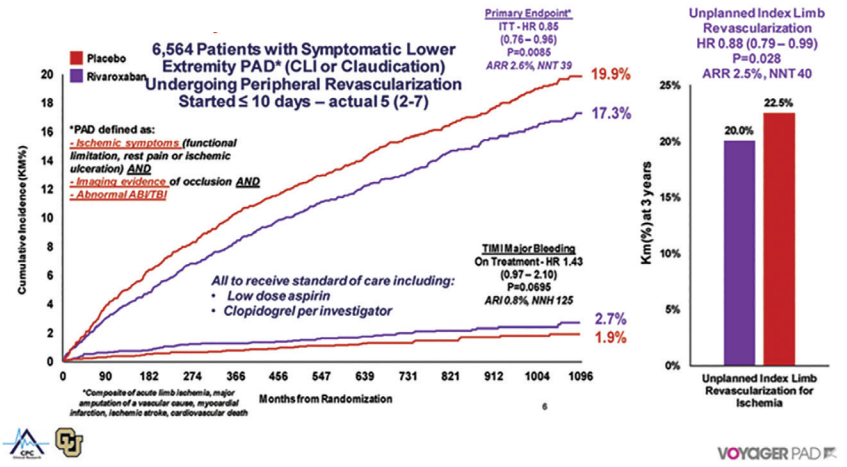

Figure 2. VOYAGER PAD Primary Results

Please describe your current PAD practice (caseload, practice setting, etc.).

I am an interventional cardiologist with a particular focus on the treatment of patients with PAD and CLI. Our practice has a particular focus on patients with CLI, which is an advanced form of PAD. More than 80% of our patient population consists of patients with CLI.

Are you currently referring patients out or receiving referrals from other clinicians for PAD patients? Describe the pathway of the PAD patient in your experience.

Our center has been identified as a regional PAD/CLI center. A sizable portion of our patients are referred to us from colleagues that also treat patients with PAD and CLI. Also, a sizable portion are patients seeking a second opinion for limb preservation after being informed that there are currently no options available to them for revascularization and the only feasible procedure to perform is a major amputation. We have noticed over the last 2 years that patients have been researching options for limb preservation and seeking a second opinion.

Please describe your current process for diagnosing and screening for PAD.

There are commonalities among clinicians in terms of evaluating and diagnosing patients with PAD and CLI. However, I believe the pathway for diagnosing patients with PAD differs from diagnosing patients with CLI. For example, an ankle-brachial index is an accepted modality for screening patients with PAD. I do not believe ABIs are an appropriate modality to evaluate patients with CLI. There have been multiple studies showing that ABIs can be falsely normal in the CLI patient population due to noncompressible, calcified arteries.[22, 23] Anecdotally we see a lot of patients with CLI presenting with advanced wounds after being told that there is no evidence of PAD. Unfortunately, there are providers who are misled by a falsely normal ABI value.

Furthermore, patients with CLI tend to have multi-vessel, multi-level disease. The use of CTA might not be ideal to evaluate bilateral infrapopliteal disease because these vessels tend to be calcified and small. There is a significant risk of under- or overestimation of disease within this anatomical segment. For that reason, we usually prefer to utilize a detailed arterial ultrasound, which I believe to be the ideal evaluation modality for patients with CLTI. However, ultrasonography depends heavily on the technical skills of the performing sonographer. In our center, most of our sonographers are interventional sonographers, who provide support in evaluation and patient procedures. Their understanding of the anatomy and the nuances of different image interpretation is essential to evaluate the degree of disease these patients suffer from. For example, all our CLI patients have their plantar circulation evaluated including the dorsalis pedis artery and medial and lateral plantar arteries. This is essential to determine the plan for treatment.

Why is screening so crucial?

Any patient presenting with a wound as the first manifestation of PAD/CLI represents a failure of the healthcare system. We believe screening patients at risk of PAD/CLI is essential in identifying those who need optimal medical therapy and/or are at risk of limb loss. Once that knowledge is established, the healthcare providers can tailor evaluation, medical therapy, and regular follow-up. Discussing the risk of ischemic wound development and signs/symptoms of CLI might make the difference between limb preservation, life preservation, and limb loss. I do believe taking steps as simple as shoes and socks off in healthcare providers' offices can identify patients with silent ischemia or in some cases wounds that otherwise would go unnoticed until it is too late. Patients with CLI and diabetes mellitus may have impaired sensation that limits their ability to sense pain or even awareness they have an open wound.

Are you working with a multidisciplinary team for the treatment of your PAD patients? If so, describe how that has improved patient care.

The concept of a multidisciplinary team is essential to the treatment of patients with CLI. However, a lot of healthcare providers seem to believe a multidisciplinary team must be housed in the same physical location. A CLI revascularization center must develop a network of highly specialized, skilled healthcare providers that can address and treat various aspects of care when seeing patients. For example, patients that undergo deep vein arterialization (DVA), a new procedure where the blood flow is diverted from the tibial artery to the adjacent tibial vein, must be referred to a podiatrist/wound

care provider who understands the physiological and anatomical changes that happen to the limb post-deep vein arterialization. Unfortunately, we have so many examples of post-DVA patients under the care of wound care specialists or podiatrists not familiar with advanced forms of CLI treatment, resulting in the patients unnecessarily losing their limbs. Similarly, vascular physicians who do not treat an appropriate number of CLI patients may lack the expertise in establishing adequate treatment strategy. Identifying those different team members who are just as passionate as you in limb salvage and preservation is essential to having a successful CLI limb preservation center.

In addition to interventions, are your putting your PAD patients on a medical therapy regimen to prevent MALE?

Patients with PAD and CLI tend to suffer from multiple comorbidities such as CAD, diabetes, and CKD. Adherence to GDMT is essential in the treatment of those patients. Because of significant overlap between the diagnosis of CLI and other comorbidities, placing patients on appropriate medical therapy is essential to their overall care. GDMT targeting specifically PAD and CLI has historically been lacking but is making great strides. The overlap is mainly related to the diffuse atherosclerotic process involving multiple vascular beds. Physicians must make sure that patients adhere to appropriate medical therapy, including antiplatelet therapy, statin therapy, and appropriate antihypertensive medications. Randomized trials have shown disappointing results when lack of adherence to medical therapy was reported.

How has data from trials such as COMPASS and VOYAGER PAD changed your practice?

The COMPASS and VOYAGER PAD trials have been a refreshing change geared specifically toward medical treatment of patients with PAD and CLI. We now know that placement of patients on 2.5 mg of rivaroxaban twice daily in patients with stable PAD has been shown to be beneficial in reducing major adverse limb events. More importantly, data from the VOYAGER PAD trial showed that patients who received the above medical regimen post-surgical and post-endovascular revascularization have shown significant reduction of major adverse limb events. These are the only trials solely dedicated to medically evaluating and treating patients with PAD and CLTI. We now have clear guidance on the appropriate antiplatelet/anticoagulation regimen. With that said, I believe adherence to this evidence-based therapy across the vascular community has been lacking. We need to emphasize the unique nature of these trials among our peers. Furthermore, we need to address reasons that may be responsible for low compliance rates among patients.

What new technology or information excites you the most about the future of PAD treatment, and what will best optimize patient care?

While there are significant challenges in the treatment of patients with PAD and CLTI, the field has been exploding with modern technologies. Over the last 10 to 15 years, a lot of these new techniques and technologies have improved our ability significantly to revascularize multi-level, multi-vessel disease and achieve adequate perfusion to ischemic limbs. I am particularly excited about the concept of percutaneous DVA. Patients with end-stage plantar disease previously had no feasible way to improve arterial flow to ischemic tissue in the foot. Data with randomized trials and our own published experience show that performing percutaneous DVA resulted in limb salvage rates as high as 60%.[21, 24] I believe the biggest challenge in the treatment of patients with advanced PAD and CLTI revolves around maintenance of patency. It is only a matter of time, as technology improves, that short- and long-term patency will increase in complex CLTI population. More importantly, amputation as a first-line therapy in patients with CLTI is becoming less acceptable.

Summary

The morbidity and mortality associated with PAD are underappreciated. PAD is associated with a threefold increase in all-cause mortality. Following a major adverse limb event, the prognosis worsens considerably, with increased risk for amputation, death, MI, or stroke. As a result, it is of paramount importance to diagnose patients early and place them on appropriate medical therapy to reduce the risk of major cardiovascular and limb adverse events. Dual pathway inhibition has been found to lower major adverse limb events by 43% and amputations by 58%. High-risk patients may have a greater net clinical benefit from dual inhibition therapy (rivaroxaban plus aspirin) than those without high-risk characteristics.

Patients with PAD need access to a variety of healthcare providers to treat differing manifestations of the disease and reduce their risk for major limb adverse events. Large academic centers often have established pathways for patients with PAD. Clinicians at smaller or regional facilities may need to build partnerships with other specialties to ensure patient-centered care. It is critical that wound care centers and podiatrists are involved in overall patient management to optimize outcomes.

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