Peripheral Artery Disease: Current Insights into the Disease, its Diagnosis and Management

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This is to acknowledge that Subhash Banerjee, M.D. has disclosed that he has financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Banerjee will be discussing off-label uses in his presentation.

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Academic and research focus: Peripheral artery disease, minimally invasive heart and vascular procedures.

Purpose: The goal of this presentation is to provide an update on recognition, clinical assessment and treatment of patients with peripheral artery disease (PAD) of the lower extremity arteries.

Overview: PAD is common, however often underrecognized. It is an important cause of morbidity particularly in older adults, those with diabetes mellitus, and smokers. Risk factors for PAD are similar to the risk factors of atherosclerosis elsewhere and modification of these risks is key to successful management of PAD. Intermittent claudication (IC) is a classic symptom of PAD, but a the vast majority of patients remain asymptomatic. PAD in patients with certain high risk features can be diagnosed by an abnormal ankle-brachial index (ABI) value. Other manifestations of PAD include critical (CLI) and acute (ALI) limb ischemia. Progression from IC to CLI is rare and prophylactic revascularization to prevent such progression is not indicated. Treatment of IC includes enrollment in a supervised walking program, use of cilostazol and, for select patients, percutaneous or surgical revascularization. Management of PAD requires an interdisciplinary team including a primary care provider.

Educational objectives: At the completion of this lecture, the learner will be able to:
1. Appreciate the risk factors and prevalence of PAD and its relationship to cardiovascular disease.
2. Understand and perform an ABI test for diagnosing PAD in appropriate patients.
3. Comprehend various clinical presentations of PAD.
4. Gain knowledge regarding the medical management and indications for revascularization (endovascular or surgical) of PAD and when this approach should be employed.

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Abstract

Peripheral artery disease (PAD) affects over 220 million individuals worldwide and approximately 12 million in the U.S. Although, a vast majority of patients with PAD remain symptomatic, the disease portends a significantly heightened risk of myocardial infarction and death in affected individuals. A thorough physical exam and an ankle brachial index test are practical and cost-effective means of diagnosing PAD. Tobacco use and diabetes mellitus are especially virulent and independent risk factors for PAD. In symptomatic individuals, PAD can result in significant disability, loss of quality of life and amputations. Although, progression from claudication to critical limb ischemia (CLI) is rare (<5%), practitioners should be able to recognize patients presenting with CLI and promptly refer them for revascularization. Dedicated secondary prevention strategies with pharmacologic and exercise therapy interventions can improve both cardiovascular and limb outcomes in PAD. Revascularization of lower extremity arteries using endovascular and surgical means is indicated when guideline directed medical therapies provide inadequate improvement in symptom status in claudicants, and for CLI and acute limb ischemia. Significant strides have been made over the last decade in providing more durable improvement in patient symptoms and limb salvage rates with endovascular procedures. These minimally invasive strategies together with an increased awareness, dedicated pharmacotherapy, an exercise regimen and an interdisciplinary approach are due to significantly alter the course of caring for patients with PAD.

Introduction

Peripheral artery disease (PAD) refers to atherosclerotic and non-atherosclerotic diseases affecting the aorta, its branch vessels, iliac, and lower extremity arteries. Atherosclerotic involvement of these arteries constitutes the bulk of patients presenting with PAD. This review provides an up to date view of the biology of PAD, its distinguishing features from coronary artery disease (CAD) and how this recognition has altered the course of therapeutic medical and minimally invasive interventions. It focuses on therapies that for the first time have provided robust and effective means to alter the course of this disabling and progressive disease.

Living Face of PAD

Imaging evidence from the Horus study described PAD in Egyptian mummies; mean age of death was 40 years and atherosclerosis of the aorta and peripheral arteries was the most common manifestation.[1] This evidence along with many others has established that PAD was commonplace in mummified Egyptians. However, diagnosing PAD during present times *in vivo* can be challenging, as most patients with PAD remain asymptomatic for prolonged periods or forever.[2] Nevertheless, such individuals are at a 3 to 4-fold increased risk of cardiovascular events.[3] The living face of PAD is a middle age individual in his or her 50s with history of tobacco use and/or diabetes mellitus (DM) or simply above the age of 65 years, with no symptoms suggestive of PAD.

Globally, PAD per the latest estimates in 2010 affects 220 million people in the world. It has seen a ~30% increase in low to middle income and a 13% increase in high-income nations over the prior decade. In the U.S. nearly 6% Americans above the age of 40 years are projected to have PAD and in some high-risk groups, the prevalence of the disease exceeds 30%. The prevalence of PAD increases with age (1% between 40-49 years compared with 15% above the age of 70 years).[4] The prevalence and severity of the disease is

disproportionately high in Black and Hispanic ethnicities.[4] Although, men are affected earlier, the overall prevalence increases proportionately with age.[5]

Although, data regarding the economic burden of PAD are scarce, the total medical costs of a U.S. Medicare patient with PAD over an index treatment quarter and the following year are over $50,000.[6] This exceeds the costs of treating CAD (~$46,000 per patient) over a similar time frame.

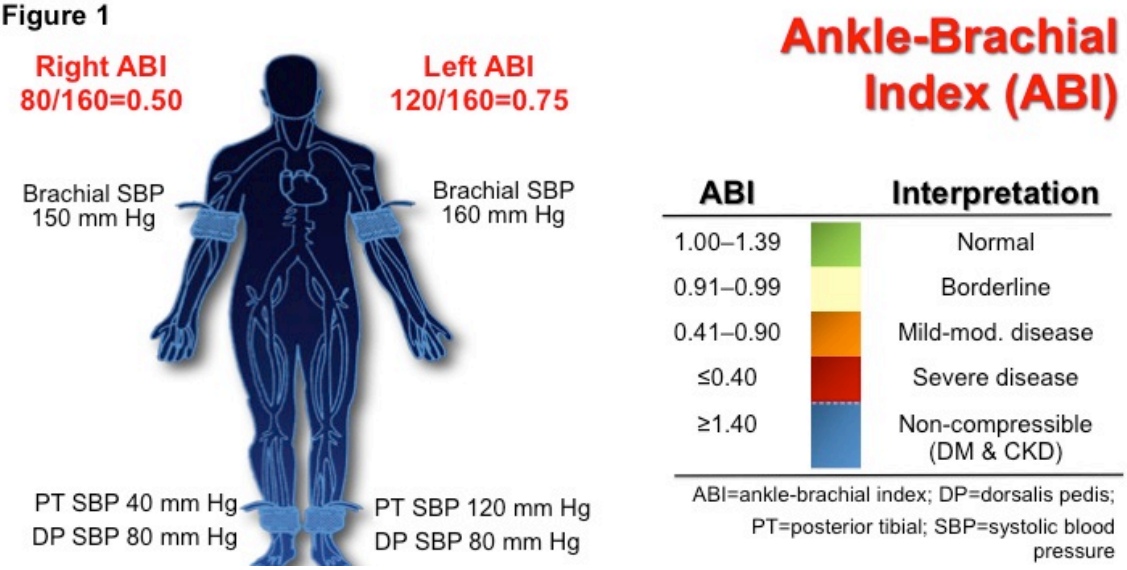
It is important to emphasize again that nearly 50% of patients affected by PAD are asymptomatic, 20-40% present with atypical leg pain and only 10%-30% experience classic intermittent claudication symptom.[2] A thorough history combined with physical examination is generally sufficient to separate claudication from mimicking conditions grouped under the term pseudoclaudication **(Table 1)**. Sixty percent of patients with PAD will have ischemic heart disease and 30% cerebrovascular disease; over 5 years 20% will experience a non-fatal cardiovascular event, 20% will die, primarily of a cardiovascular cause and 1-3% will undergo an amputation.[7, 8] As stated earlier, progression to critical limb ischemia (CLI) is rare. Fewer than 5% of patients with PAD will advance to CLI.[5] However, overall survival is worse than for many cancers. One-year risk of limb amputation is 30%, 10% will experience a fatal cardiovascular event and 5-year all-cause mortality is 50%.[5, 9] These facts are sobering and indicate the importance of timely diagnosis and treatment of PAD.

Establishing the Diagnosis of PAD

In a minority of patients with PAD, aching of leg muscles reliably reproduced by walking a set distance and relieved promptly (in a few minutes) upon rest can be elicited. These symptoms consistent with intermittent claudication are never present at rest or exacerbated by change in position. Occlusion or severe stenosis of the distal aorta often result in bilateral buttock, thigh and calf pain, whereas lesions involving the iliac, common femoral and the superficial femoral artery (SFA) result in unilateral buttock, thigh and calf claudication. Patient symptoms and a physical exam are not extremely reliable

tools to diagnose PAD. Careful documentation of the distance walked until onset of symptoms is recommended, as it allows a more objective documentation of disease progression and any impairment in the quality of life (QOL).

Figure 1

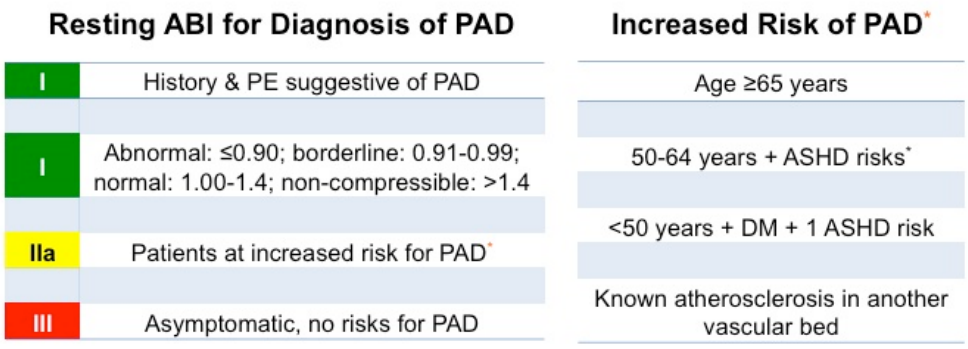


Targeted diagnostic testing with an ankle-brachial index (ABI) measurement can be used to establish the diagnosis of PAD. ABI for a given lower limb can be easily ascertained by dividing the higher of the dorsalis pedis and posterior tibial artery systolic pressures recorded using a continuous-wave Doppler probe, by the higher of the two brachial artery systolic pressures **(Figure 1)**. ABI is considered normal between 1.00 -1.39, borderline between 0.91 - 0.99, abnormal at ≤0.90 and ≥1.40 **(Table 2)**. An abnormal ABI is diagnostic for PAD.[9] ABI values ≥1.40 is attributed to non-compressibility of the vessels secondary to extensive medial calcification associated with advanced age, DM and/or chronic kidney disease (CKD).[10] In this setting, when ABI values can be falsely elevated or false normal, a toe-brachial index (TBI) should be measured, as toe vessels are less susceptible to stiffening. A TBI value <0.70 is consistent with the diagnosis of PAD.[10] No study has yet demonstrated that treatment(s) initiated due to risk reclassification made on the basis of ABI findings, over traditional cardiovascular risks have benefited patients, and one study showed a non-significant trend toward increased risk for major bleeding with aspirin therapy

in such individuals. This applies to asymptomatic adults without known diagnosis of PAD, CAD, severe CKD, or DM. For such individuals, the 2013 U.S. Preventive Services Task Force (USPSTF) statement found insufficient evidence to recommend ABI test for PAD screening.[11]

Therefore, screening for PAD with a resting ABI is recommended for patients with history or physical examination suggestive of PAD and at a high risk of PAD **(Figure 2)**.[12] Individuals at high risk of PAD include those ≥65 years, between 50 and 64 years and known risk factors for atherosclerotic heart and vascular disease (hypertension, hyperlipidemia, DM, smoking or family history of PAD), less than 50 years of age with DM and at least one-atherosclerosis risk factor or know atherosclerotic vascular disease in another vascular bed.

Figure 2: ABI: Who should be screened for PAD?



In addition to ABI, pulse volume recordings (PVR), Duplex ultrasound, computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) could be used as adjunctive tests during the evaluation and treatment of patients with PAD. These tests are not indicated for screening asymptomatic patients for PAD.[13]

The severity of PAD can be classified according to either the Fontaine or Rutherford categories **(Figure 3)**. These categories are commonly used in research and clinical studies, however may also be very useful in delineating

patient symptoms and presentation in clinical settings.[14]

Figure 3: Classification of PAD

Fontaine

Stage	Clinical
I	Asymptomatic
IIa	Mild claudication
IIb	Moderate-severe claudication
III	Ischemic rest pain
IV	Ulceration or gangrene

Rutherford

Category	Clinical
0	Asymptomatic
1	Mild claudication
2	Moderate claudication
3	Severe claudication
4	Ischemic rest pain
5	Minor tissue loss
6	Ulceration or gangrene

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Clinical outcomes of patients with PAD

Patients with PAD are at an increased risk for cardiovascular ischemic events (CAD and cerebrovascular disease).[15] Moreover, cardiovascular events are more frequent than ischemic major adverse limb events (MALE). There is approximately a 2 to 4-fold excess of CAD and cerebrovascular disease in patients with lower extremity PAD. Approximately 12% to 25% of patients with lower extremity PAD have hemodynamically significant carotid artery stenosis and the severity of lower extremity PAD correlates with the severity and extent of significant carotid artery stenosis. A third of men and fourth of women with known CAD or cerebrovascular disease have lower extremity PAD. Obstructive CAD in patients with PAD is present in ~72% of patients. These estimates vary according to the tests and definitions used in various studies.[16] In PAD patients, the risk for non-fatal myocardial infarction (MI) is increased by 20-60%; the risk of death is increased 2 to 6- fold, and of stroke by an approximate 40%. The annual mortality rate of patients with lower extremity PAD is 4-6%.[17] It is highest in patients with advanced PAD and CLI. Here, it is also important to indicate that claudication symptoms usually remain stable and do not rapidly worsen or improve and progression from stable claudication to CLI or acute limb ischemia (ALI) is rare (1-2% over 5 years).[13] Mortality rates in CLI can be as high as

20% within 6 months from diagnosis and >50% at 5 years.[18] For non-revascularizable or 'no-option' CLI patients 1-year mortality can be up to 40%.

SFA in not LAD

PAD had long being treated as an orphan disease and an afterthought coronary technology backwater. Medical and minimally invasive revascularization therapies developed primarily for patients with CAD was been applied to patients with PAD. However, the last decade has seen a remarkable growth in our understanding of the biology of peripheral artery atherosclerosis that in-turn has fueled an unrivaled growth in the discovery of medical and interventional therapies to reduce major adverse cardiovascular events (MACE) and MALE. **Table 3** summarizes key differences between coronary and peripheral artery atherosclerosis.[19] The following section will highlight key therapeutic advancements that have the potential to fundamentally alter the course and prognosis of patients with polyvascular atherosclerotic disease. Such patients could be advised an optimal combination from the following options: healthy lifestyle, low-dose aspirin, P2Y12 inhibitor, high intensity statin and angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). In addition, we could now consider addition of a proprotein convertase subtilisin/kexin-9 (PCSK9) inhibitor, canakinumab (monoclonal antibody against interleukin (IL-) 1β), empagliflozin, a sodium glucose co-transporter 2 inhibitor or SGLT2 inhibitor, vorapaxar (protease activated receptor or PAR 1 receptor antagonist) and low dose rivaroxaban (factor Xa inhibitor).[20]

Medical therapy for PAD

The 2016 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines have provided a timely update to medical therapy recommendations from the 2011 ACC/AHA PAD guidelines.[12] It recommends the use of statins and antiplatelet therapy such as aspirin or clopidogrel. The new guideline also indicates clinical situations when dual-antiplatelet therapy (DAPT) may be considered (after vascular surgery or endovascular procedures). Patients are also recommended to participate in a structured exercise program, which

should be individualized to the patient and should include specific instructions for the type, frequency, intensity and duration of exercise. Although, supervised exercise is the most effective form of structured exercise, other options in the guideline include home- or community-based walking exercise or alternative forms of exercise such as upper-body exercises. These recommendations for supervised exercise now have greater relevance, given the recent determination by the Centers for Medicare & Medicaid Services to cover supervised exercise therapy for beneficiaries with intermittent claudication for the treatment of symptomatic PAD (up to 36 sessions over a 12 week period).[21] The new guideline also strongly advises patients with PAD to avoid second-hand smoke and to get an annual flu shot to avoid cardiovascular complications of flu. In addition to these established therapies, newer pharmacotherapies have shown great promise in the treatment of patients with PAD. Herein, we provide a brief summary of the evidence recently approved by the U.S. Food and Drug Administration (FDA) for emerging drug interventions for PAD. The level of ACC/AHA guideline recommendation is included within brackets along with each recommendation.

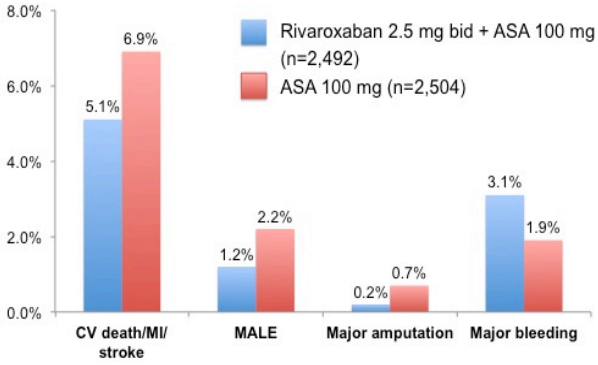
Antithrombotic therapy

Antiplatelet therapy with aspirin alone (range 75–325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce MI, stroke, and vascular death in patients with symptomatic PAD (I). In asymptomatic patients with PAD (ABI ≤0.90) an antiplatelet therapy is reasonable (IIa). DAPT may be used following revascularization procedure for PAD (IIb).

Vorapaxar is an oral PAR-1 antagonist. It inhibits thrombin-induced platelet activation and was studied for secondary prevention in patients with prior MI, PAD and ischemic stroke in the TRA 2°P-TIMI 50 trial. In this study of 26,449 subjects, vorapaxar was compared with placebo and it showed a significant reduction in the occurrence of cardiovascular death, MI, or stroke.[22] This improvement was accompanied by an increase in the incidence of moderate or severe bleeding and intracranial hemorrhage (ICH); the latter increased primarily in patients with prior stroke. As a result, the study therapy was discontinued in all

patients with a history of stroke. The drug received FDA approval in 2014 for the reduction of thrombotic cardiovascular events in patients with prior MI or PAD. Vorapaxar is contraindicated in patients with a prior history of stroke or transient ischemic attack (TIA). In the FDA label cohort at 3 years vorapaxar significantly reduced the composite endpoint of cardiovascular death, MI or stroke compared with placebo (7.9% vs. 9.5% p<0.001).[23] It however increased GUSTO moderate or severe bleeding (3.7% vs. 2.4%, p<0.001). In the overall cohort of 5,845 PAD patients, vorapaxar significantly reduced the need for peripheral revascularization (19.3% vs. 15.4%, p = 0.003).[24] Based on this evidence, the PAD guidelines give IIb recommendation to the use of vorapaxar. Use of ticagrelor in the Evaluation of Ticagrelor in Peripheral Artery Disease (EUCLID) trial showed no additional benefit over clopidogrel in patients with stable PAD.[25] Currently, there are no recommendations for the use of ticagrelor in PAD. Recently, the COMPASS trial (n=27,395) with CAD and/or PAD that included rivaroxaban with or without aspirin,, rivaroxaban in combination with aspirin significantly reduced the risk of MACE by 24%.[26] In the PAD sub-population, the same combination reduced MALE including major amputation by 46%, as was the combination of MACE or MALE by 31%.[27] Low dose rivaroxaban is currently under evaluation by the FDA for approval **(Figure 4)**.

Figure 4: COMPASS: Rivaroxaban Reduces CV and Limb Events in PAD



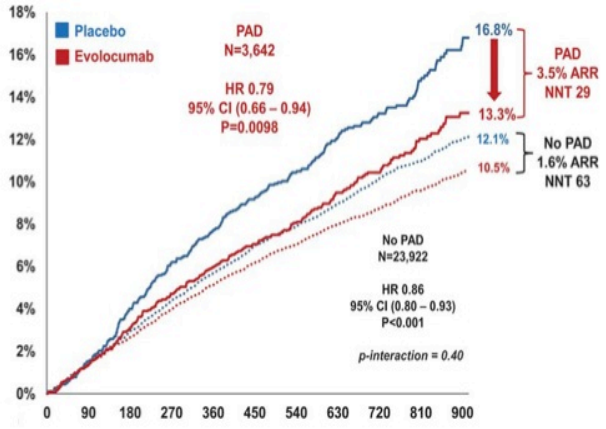
Lipid-lowering therapy

Statins in patients with PAD reduce cardiovascular events and mortality, although much of the data regarding this, stem from cardiovascular studies.[28] Few randomized trials have shown that statins improve pain-free walking distance or pain-free walking time.[29] The magnitude of this effect has been

small and the studies were limited in size. In the REACH registry, statin use was associated with an 18% lower rate of adverse limb outcomes, including worsening symptoms, peripheral revascularization, and ischemic amputations.[30] The ACC/AHA 2016 guidelines provide a class I recommendation for the use of statins in all patients with PAD.[12]

The FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) included27,564 patients with atherosclerotic disease on statin therapy randomized to evolocumab or placebo and followed for a median of 2.2 years.[31] Evolocumab is a PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor. It reduced low-density lipoprotein cholesterol and cardiovascular events in the trial. Patients with PAD (n=3,642, or 13.2% of the overall study population) were included if they had intermittent claudication and an ABI <0.85, or a prior peripheral vascular procedure. In the PAD cohort, the primary endpoint, a composite of cardiovascular death, MI, stroke, hospital admission for unstable angina, or coronary revascularization was significantly reduced by evolocumab (hazard ratio [HR] 0.79; 95% confidence interval [CI], 0.66–0.94; P=0.0098).[32] PAD patients had a larger absolute risk reduction for the primary end point (3.5% with PAD, 1.6% without PAD) and the study drug reduced the risk of major adverse limb events in all patients (HR, 0.58; 95% CI, 0.38–0.88; P=0.0093). Moreover, lower low-density lipoprotein cholesterol levels (down to <10 mg/dL) were associated with a lower risk of limb events. PCSK9 inhibitors are currently not approved for the indication of PAD **(Figure 5)**.

Figure 5: PCSK9 Inhibition in PAD: FOURIER Trial



Glycemic control

Poor glycemic control is an independent risk factor for PAD.[33] Management of DM in a patient with PAD is critical and should be coordinated between members of the healthcare team (ACC/AHA guideline recommendation I). Glycemic control can be beneficial for patients with CLI to reduce limb-related outcomes (II). In the UK Prospective Diabetes Study (UKPDS) trial, optimization of blood glucose levels prevented peripheral neuropathy and PAD in patients with type 2 DM.[34] A reduction in HBA1c of 1% was associated with a reduction in risk of 43% for amputation or death from PAD. A new class of anti-diabetes medication, sodium glucose cotransporter-2 (SGLT2) inhibitor (empagliflozin) has shown favorable effects in patients with PAD. SGLT2 facilitates ~90% of renal glucose reabsorption. Its inhibition increases renal urinary glucose excretion, resulting in a reduction of plasma glucose levels in an insulin-independent manner. In the vulnerable subgroup of patients with type 2 DM and PAD in the EMPA-REG OUTCOME trial, empagliflozin reduced mortality, hospitalization for heart failure and progression of renal disease with no increase in the risk of lower limb amputation.[35] The reduction in cardiovascular death with the drug translates to a number needed to treat of 29 patients over 3.1 years to prevent 1 event.

Peripheral artery revascularization

Aortoiliac disease

Endovascular therapy is generally recommended as the first line treatment for short and focal or Transatlantic Societal Consensus TASC type A or B aortoiliac lesions and achieves 1-year primary patency rates of >95%.[36] Treatment options include primary stenting (using balloon expandable or self-expanding uncovered or covered stents) or balloon angioplasty with selective stenting. Outcomes of endovascular intervention for aortoiliac disease improve with the use of covered stents with the primary benefit being a reduction in restenosis. Covered stents also offer protection against arterial rupture when used in the treatment of heavily calcified lesions.

The most common approach is direct aortofemoral bypass grafting using a bifurcated prosthetic conduit. This is a major surgical procedure with an operative risk in the range of 1–4% and excellent long-term durability (typical 5-year patency rates of >85%; **Figure 6**).[36]

Figure 6: Surgical vs. Endovascular Repair

Aortoiliac PAD		
Outcomes	**Aortofemoral bypass**	**Endovascular repair**
30-day mortality	2-3%	<1%
Perioperative cardiac complications	2-7%	<2%
Perioperative renal complications	1-4%	0-6%
Perioperative pneumonia	1-11%	<2%
1-year primary patency	92-97%	70-97%
5-year primary patency	80-95%	60-86%

Patency of the common femoral and profunda femoris arteries is of central importance to long-term limb preservation and function. Direct surgical endarterectomy of the common femoral artery is a low risk, effective, and durable procedure that can be performed in isolation or combined with treatment of aortoiliac or FP disease in a variety of hybrid procedures.[37]

Femoropopliteal (FP) disease

The superficial femoral artery (SFA) is commonly involved in patients with intermittent claudication or CLI. Extensive SFA and /or multilevel occlusion are often observed in patients with CLI. Endovascular treatment of FP disease is very widely performed with growing procedure volumes due to high technical success rates and low peri-procedural complications and morbidity compared with open surgical options. Despite high technical success, durability has been variable and long lesion length (≥20 cm), chronic total occlusions (CTO), popliteal artery involvement, extensive calcification, and small caliber (≤5 mm) arterial disease are linked to poor outcomes.[38] Therefore when symptoms are advanced or prior endovascular treatments have failed, open surgical bypass grafting provides an effective and more durable alternative to endovascular treatment. When surgical revascularization is performed, bypass to the popliteal artery with autogenous vein is recommended in preference to prosthetic graft

material. Femoral-tibial artery bypasses with prosthetic graft material should not be used for the treatment of claudication **(Figure 7)**.[12]

Figure 7: Infrainguinal Peripheral Artery Revascularization

	Femoropopliteal	Infrapopliteal
Approach	**Patency**	**Patency**
Surgical		
Vein bypass	65-75% at 5y	65-70% at 5y
Prosthetic bypass	30-60% at 5y	10% at 5y
Endovascular		
Balloon angioplasty	30-60% at 1y	25-65% at 1y
Bare-metal stents	50-80% at 1y	-
Covered stents	45-70% at 1y	-
Atherectomy	70-80% at 1y	70-80% at 1y

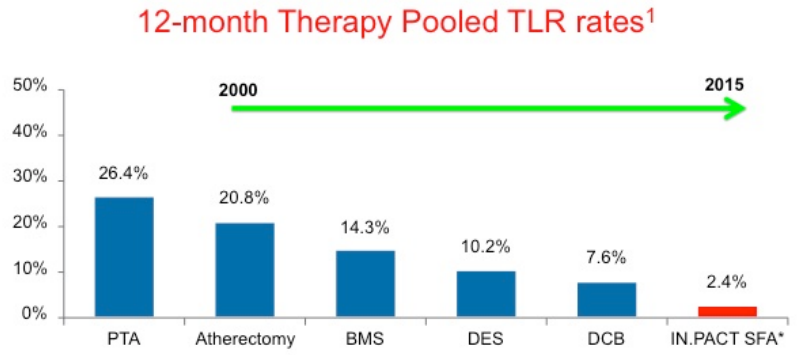
Mainstays of endovascular treatment of FP disease include balloon angioplasty, cryoplasty, stenting, and atherectomy. A vast majority of these trials were conducted for obtaining device indications and in patients with intermittent claudication and moderate severity of PAD (lesion lengths <15 cm and limited number of CTO). As durability with conventional balloon angioplasty has been poor, stenting is often used to treat more complex FP PAD. Nitinol self-expanding bare-metal stents (BMS) use is the FP segment is supported by numerous clinical trials and has been the primary modality for over the past decade. Stent fracture, stent thrombosis and moderately high in-stent restenosis (ISR) have been its major limitations.[38] Nevertheless, it was a significant advancement over balloon angioplasty with restenosis rates significantly lower at 3, 6, and 12 months. Newer generation self-expanding stents such as the biomimetic (SUPERA) stents designed to accommodate high biomechanical stresses have shown excellent results in SFA and proximal popliteal artery lesions, with 86% patency and no fractures at 1 year. Flexible polytetrafluoroethylene (PTFE) lined nitinol stent grafts (VIABAHN) has been successfully used to treat de novo, ISR and long (≥20 cm) and chronic total occlusions (CTO) of the FP artery with higher success compared with BMS (70% patency vs. 40% at 1 year). The VIABAHN stent is also used to treat vascular complications such as dissections or perforations.[38]

Drug (paclitaxel)-eluting flexible nitinol polymer free self-expanding stent (Zilver PTX DES) for the FP artery (average length 6.5 cm) was approved for clinical use in 2012. The results of a randomized trial of 474 patients assigned to

either Zilver PTX or balloon angioplasty with provisional stenting showed that the DES group had substantial improvements in 12-month event free survival and primary patency compared with the control group, and these benefits were sustained for 5 years **(Figure 8)**.[39]

To overcome the limitations associated with permanent endovascular prosthesis in a highly dynamic artery, 'stent-free' strategies involving atherectomy and drug-coated balloon (DCB) have been adopted widely. While large randomized clinical trials testing the role of various atherectomy (plaque excision) strategies have been lacking, the evidence base to support the use of DCB in FP artery is robust and durable **(Figure 8)**.[39]

Figure 8: Endovascular Treatment of PAD

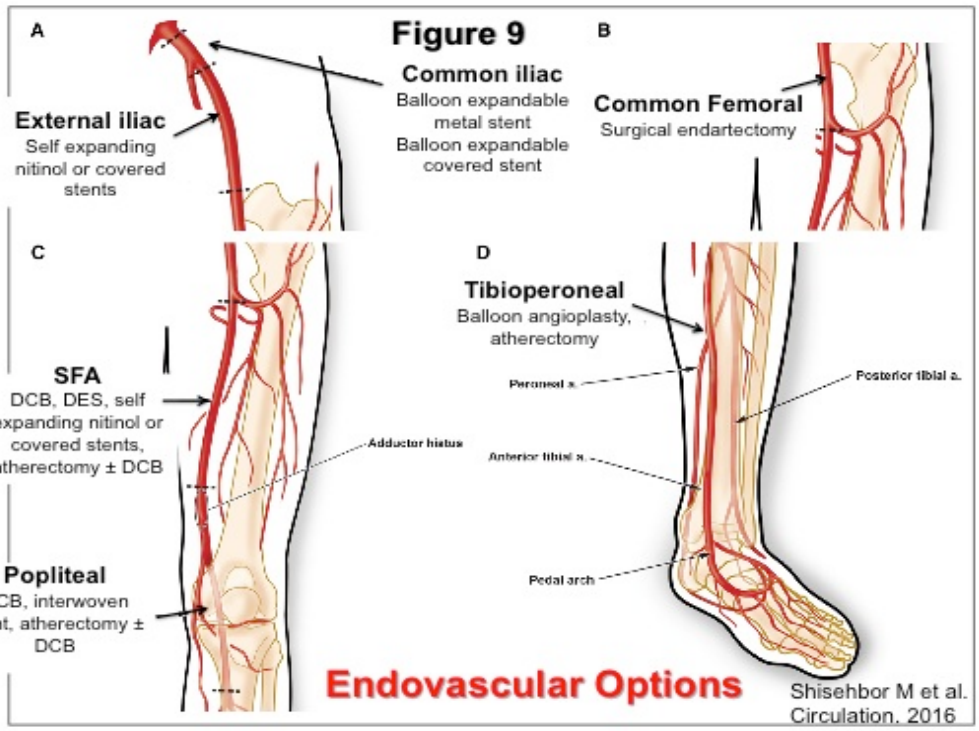


Based on this summary evidence, the ACC/AHA 2016 guidelines give a level I indication for endovascular treatment of hemodynamically significant aortoiliac lesions and IIa for femoropopliteal lesions in claudicants. Prophylactic endovascular indication to prevent progression to CLI is contraindicated (III).[12]

Below-the knee (BTK) PAD

PAD of the tibioperoneal and pedal arteries constitute a challenging anatomic location for endovascular therapy. Often involved in patients with CLI, and revascularization of these arteries are often performed for wound healing and limb salvage indications. Establishing a 'straight line' uninterrupted flow to the foot or providing maximal perfusion to an involved angiosome are both employed in clinical practice. BTK revascularization also presents significant technical challenges such has retrograde peripheral artery or pedal artery access and proficiency with various advanced endovascular skills and devices. Above all, to achieve desired clinical success and avoid amputations, BTK artery

revascularization needs to be accompanied with optimal wound care, medical therapy, podiatry and foot care and rigorous clinical follow-up and a motivated patient. Centers specializing in such care are now being organized as CLI centers and involve a diverse group of specialists. The area of BTK artery revascularization and wound healing is an area of great-unmet need and intensive efforts are currently underway in establishing best practice for caring for such patients and developing novel treatment strategies. Since the BASIL trial nearly two decades ago, the ongoing BEST-CLI trial is an interdisciplinary effort to compare best endovascular to best surgical revascularization therapies in CLI.[38] Balloon angioplasty and atherectomy are the only approved endovascular revascularization therapies for BTK arteries. DCB use for this location was not associated with favorable outcome and the sponsor abandoned the application of this technology in the vascular distribution. Coronary DES is



rarely used for ‘bail-out’ indications in this vascular distribution. Endovascular procedures are recommended to establish in-line blood flow to the foot in patients with non-healing wounds or gangrene. A staged approach to endovascular procedures is reasonable in patients with ischemic rest pain.[12] A summary of endovascular therapies is depicted in **Figure 9.**

When surgery is performed for CLI, bypass to the popliteal or infrapopliteal arteries (i.e., tibial, pedal) should be constructed with suitable autogenous vein. In patients with CLI for whom endovascular revascularization has failed and a suitable autogenous vein is not available, prosthetic material can be effective for bypass to the below-knee popliteal and tibial arteries.[12]

Health economic considerations

Patients with symptomatic PAD incur significantly higher medical resources and costs when compared with matched controls. As the epidemic of DM and obesity continues, the prevalence of symptomatic PAD is expected to increase. The use of evidence-based secondary prevention therapies is low; however the cost of device-based revascularization per capita is on the rise. A major goal of the ongoing US healthcare reform is to reduce wasteful spending while improving quality, resulting in the so-called value-based health care. As an integral component of this initiative, the bundled payments for care improvement to healthcare institutions and providers will drive identification of tools that are cost-effective and provide the best long-term outcomes for patients affected by PAD.

Emerging technologies

The field of PAD is in the midst of rapid growth and transformation. These include new stent designs, novel endovascular approaches and techniques and fast-pace development of cell-based and growth factor therapies for neovascularization.[37] New biomimetic stents are being designed to mimic the natural flow dynamics of peripheral arteries. Bioresorbable stent application in the peripheral arteries could help treat the stenosis and eventually be completely broken down by the body. Endoprosthesis to provide arterio-venous to arterial bypass conduit around a long occluded SFA is currently undergoing clinical trial. Localized drug delivery using nanoparticles with biological ligands could help achieve targeted delivery and potentially reduce the antiproliferative drug load on current generation devices. In CLI, potentiation of neovascularization to repair

ischemic tissue with administration of growth factors or mesenchymal stromal cells is being developed.

Finally, improved awareness, education and training of health care providers, combined with a multidisciplinary team approach to care for patients with advanced disease, will be critical to improve long-term outcomes for patients with PAD.

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Table 1: Differential diagnosis of intermittent claudication

Clinical conditions	Differential diagnosis
Intermittent claudication	Exercise induced buttock, thigh or calf pain relieved promptly at rest
Pseudoclaudication	
Spinal stenosis	Relieved by position change, sitting, laying down or flexing forward. May be associated with leg weakness
Osteoarthritis	Pain not relieved promptly with rest
Lumbar nerve compression	Positive passive straight leg raise test
Chronic compartment syndrome	In athletes with large, developed calf muscles that swell during activity leading to increased compartment pressure and decreased venous return. Pain occurs with strenuous exercise only and is relieved with rest after a long recovery period
Popliteal entrapment syndrome	Abnormal insertion of the medial gastrocnemius muscle head in young athletes, which causes compression of the popliteal artery. Tibial pulse disappears with knee extension. Pain during walking, but not with running when knee extension is not as severe
Venous claudication	History of deep vein thrombosis, edema and venous stasis skin changes. Relief of leg pain with elevation
Buerger's disease (thrombangitis obliterans)	Associated primarily with young male smokers

Reflex sympathetic dystrophy	Burning superficial pain distributed along a somatic nerve and often related to a past extremity trauma
Diabetic neuropathy	Pain is due to peripheral neuritis with accompanying skin discoloration and diminished pulses. Differentiation from intermittent claudication difficult, may require extensive neurologic evaluation

Table 2: Ankle-brachial index

Values	Interpretation
1.00 – 1.39	Normal
0.91 – 0.99	Borderline
0.41 – 0.90	Mild to moderate PAD
≤0.40	Severe PAD
≥1.40	Non-compressible ABI

Table 3: Comparison of femoropopliteal and coronary arteries

	Femoropopliteal artery	Coronary artery
Location	In a fibromuscular canal	Epicardial or intramuscular
Artery type	Muscular	Muscular
Biomechanics	Prone to extension, compression, flexion & torsion	Limited compression and flexion
Plaque characteristics	Fibrotic with few foam cells, macrophages and limited lipid rich necrotic core	Greater abundance of foam cells, smaller lipid-rich necrotic core, and greater intraplaque hemorrhage
Thrombosis	Superficial plaque erosion and eruption of calcific nodules are common causes of thrombosis in peripheral plaques	Typically results from plaque rupture
Extracellular matrix proliferation	Exuberant	Limited
Medial calcification	Extensive	Limited
Constrictive remodeling	Frequent and predominant	Observed in <15% of stable lesions