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REVIEW

Lower extremity amputation in peripheral artery disease: improving patient outcomes

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Abstract: Peripheral artery disease affects over eight million Americans and is associated with an increased risk of mortality, cardiovascular disease, functional limitation, and limb loss. In its most severe form, critical limb ischemia, patients are often treated with lower extremity (LE) amputation (LEA), although the overall incidence of LEA is declining. In the US, there is significant geographic variation in the performing of major LEA. The rate of death after major LEA in the US is approximately 48% at 1 year and 71% at 3 years. Despite this significant morbidity and mortality, the use of diagnostic testing (both noninvasive and invasive testing) in the year prior to LEA is low and varies based on patient, provider, and regional factors. In this review we discuss the significance of LEA and methods to reduce its occurrence. These methods include improved recognition of the risk factors for LEA by clinicians and patients, strong advocacy for noninvasive and/or invasive imaging prior to LEA, improved endovascular revascularization techniques, and novel therapies.

Keywords: peripheral artery disease, lower extremity amputation, mortality

Background

Lower extremity peripheral artery disease (LE PAD) is a prevalent condition in the US, affecting approximately 8 million Americans.[1,2] Although about 50% of patients with PAD are asymptomatic (Rutherford classification 0; Table 1), they are at an increased risk of mortality, myocardial infarction (MI), and stroke.[3–6] The most frequent clinical manifestation of PAD is intermittent claudication (Rutherford classification 1–3; Table 1), which is defined as leg pain with exertion that improves with rest. Patients with intermittent claudication suffer from significant functional limitations in their daily activities, and over a 5-year period approximately 5% of these patients progress to LE amputation (LEA).[7,8] The most severe manifestation of PAD is critical limb ischemia (CLI) (Rutherford classification 4–6; Table 1), which is associated with a 1-year mortality rate of 20% and a 1-year limb loss rate of 20%.[1,9] Despite the significant health burden it poses,[10] public knowledge is poor, and underdiagnosis and undertreatment of CLI are frequent until limb symptoms become severe.[11]

Once PAD is diagnosed, guidelines recommend treatment with cardioprotective medications (such as an antiplatelet agent and statin), exercise training, and risk factor modification (Figure 1).[12] Many patients remain symptomatic despite these measures and undergo LE revascularization procedures to improve blood flow, minimize symptoms, and improve quality of life. Over the past two decades, surgical intervention (LE bypass and/or endarterectomy) has largely been supplanted by endovascular intervention (atherectomy, angioplasty, and/or stenting) as the most common revascularization

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Table 1 Peripheral artery disease symptom classification: Fontaine stages and Rutherford categories

Fontaine classification		Rutherford classification	
Stage	**Symptoms**	**Category**	**Symptoms**
I	Asymptomatic	0	Asymptomatic
II	Intermittent claudication	1	Mild claudication
		2	Moderate claudication
		3	Severe claudication
III	Ischemic rest pain	4	Ischemic rest pain
IV	Ulceration or gangrene	5	Ischemic ulceration (minor tissue loss)
		6	Ischemic gangrene (major tissue loss)

choice for patients with PAD. Although the complication rate and overall morbidity associated with endovascular intervention are lower when compared with surgical revascularization, the durability and need for repeat intervention remain a significant challenge for endovascular treatment. LEA is generally reserved for situations where medical or revascularization options do not exist, when significant tissue loss has occurred, or when optimal medical therapy and/or revascularization fail. It is often considered as a last resort because it is associated with substantially higher morbidity, mortality, and health care costs.[13,14]

Multiple groups have addressed the importance of preventing LEA. However, it is important to note that standardized definitions for LEA vary in the literature. The National Institute for Health and Clinical Excellence (NICE) guidelines focus on amputation at different levels of the LE (eg, toe, metatarsal, below the knee amputation [BKA], and above the knee amputation [AKA]).[15] The Peripheral Academic Research Consortium (PARC), a consortium of academic experts and representatives from industry and the US Food and Drug Administration, has also attempted to standardize definitions of LEA (submitted; unpublished). A minor amputation is defined as any procedure that results in amputation below the ankle, including the foot or toe(s). A major amputation is defined as any procedure that results in amputation at the level of the ankle or above, and is further divided based on its location in relation to the knee. BKA is an amputation affecting the tibia at any point below the knee and above the ankle. AKA is an amputation above the knee, affecting the femur at any level.

The rates of LEA in the US are unacceptably high. A recent analysis of US Medicare data from 2000 to 2008 found that out of approximately three million patients hospitalized with PAD, 186,338 underwent major LEA during that time (6.8%).[16,17] The patients who underwent major LEA had mortality rates that were nearly twice as high as those who did not undergo major LEA at 30 days (13.5% versus [vs] 6.9%), 1 year (48.3% vs 24.2%), and 3 years (70.9% vs 43.2%) (Figure 2).[16] These striking rates of mortality in

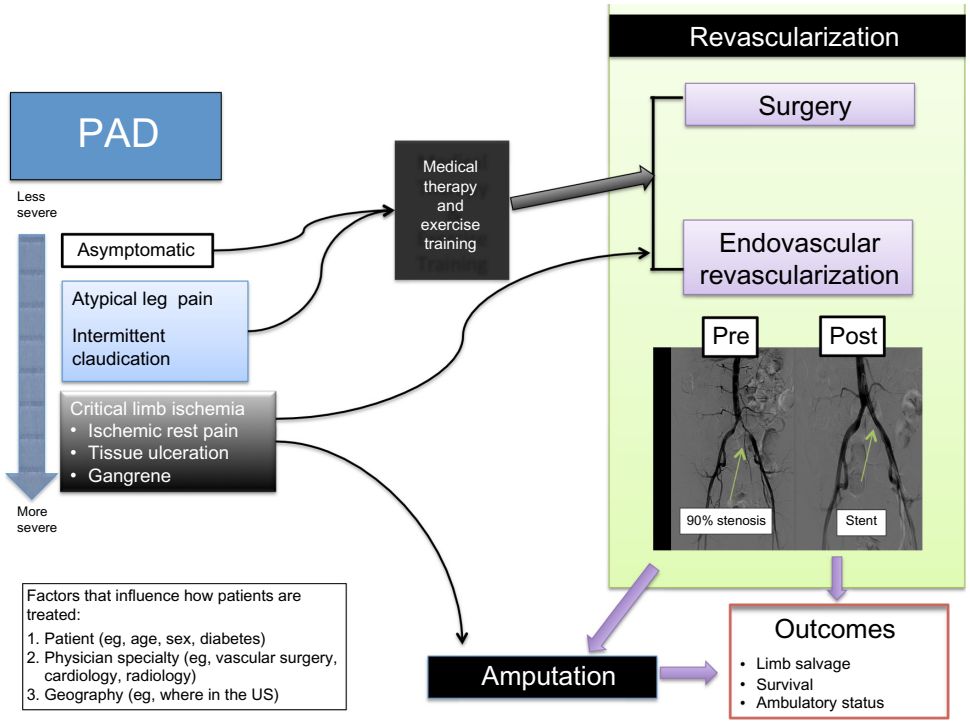

Figure 1 Conceptual framework of treatment of patients with peripheral artery disease (PAD).

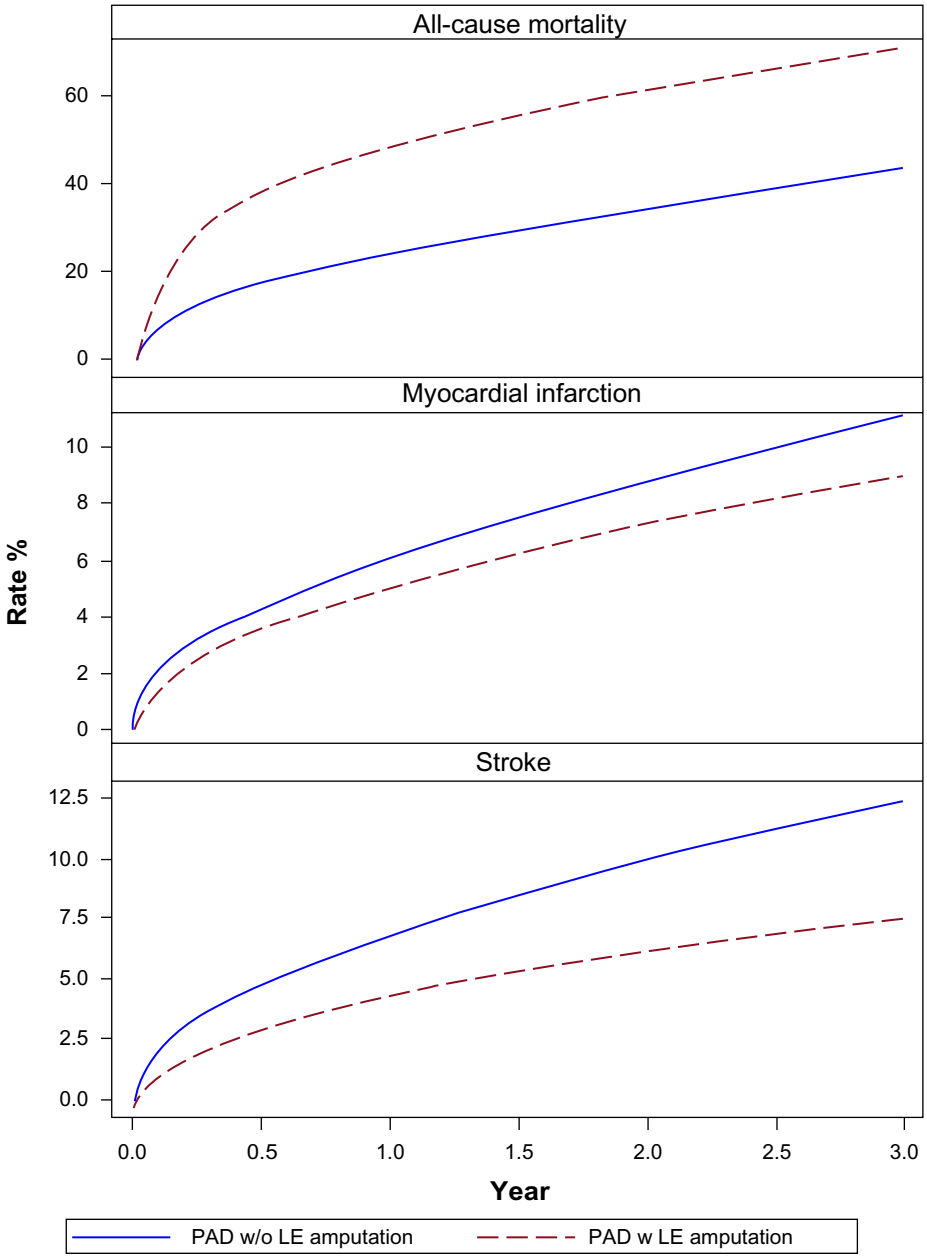

Figure 2 Clinical outcomes after lower extremity (LE) amputation. The occurrence of death, myocardial infarction, and stroke in patients hospitalized for peripheral artery disease (PAD) with and without major LE amputation: cumulative incidence rates of all-cause mortality (top panel), myocardial infarction (middle panel), and stroke (bottom panel) after major LE amputation.

Note: Reprinted from *Am Heart J*. Vol. 165(5). Jones WS, Patel MR, Dai D, et al. High mortality risks after major lower extremity amputation in Medicare patients with peripheral artery disease. Pages 809–815. © 2013, with permission from Elsevier.[16]

Abbreviations: w/o, without; w, with.

patients with PAD, with and without major LEA, highlight the need for programs to improve public awareness and standardize treatment strategies for the prevention of LEA.

Are all amputations equal?

Characteristics of both the patient and the provider can influence the decision to perform an LEA, as well as outcomes following LEA. Patient risk factors that contribute to the decision to perform LEA include the severity of symptoms and the burden and duration of PAD. Some patients with CLI present with rest pain, which is foot and/or digit pain at rest that is relieved with dependency (Rutherford classification 4; Table 1). Other patients with CLI present with tissue loss, ranging from ulceration (Rutherford classification 5; Table 1) to gangrene (Rutherford classification 6; Table 1). LE arterial anatomy is also a factor in performing LEA, although its impact has been poorly studied. Although a simple risk prediction score for arterial anatomy does not exist, a risk

score from the Project of Ex-vivo Graft Engineering via Transfection III (PREVENT III) study is a useful tool to predict amputation-free survival prior to revascularization in CLI patients.[18] Similar to this PREVENT III risk score, a Medicare report found that compared with patients with PAD who did not undergo LEA, those who underwent LEA were more likely to be male, African American, have diabetes, and have renal disease.[16,17] Patient features that were associated with increased mortality after LEA included advanced age, heart failure, renal failure, cancer, and chronic obstructive pulmonary disease.[16]

One important provider characteristic is geographic location. Review of Medicare data showed significant geographic variation in the rates of LEA across the US (Figure 3).[17] This may be due, in part, to a lack of uniform treatment algorithms to determine either the need for LEA or the level of LEA. This is important because AKA has been associated with a significantly higher hazard of death compared with more distal locations (3-year mortality rate of 76.6% for patients undergoing AKA when compared with 63.1% in patients undergoing BKA).[16] Goodney et al[19] reviewed Medicare claims data of over 18,000 patients to determine the average inpatient cost in the year prior to amputation. They found that this cost varied widely based on geographic region (from $11,077 to $42,613), and higher spending was associated with more revascularization procedures.[19] Conclusions from this study about the effects of regional spending on LEA rates are difficult to make, as all patients in this study had an LEA.

Although the need for LEA is likely evidence of an elevated cardiovascular risk in these patients rather than the cause of substantial morbidity and mortality, awareness of the dramatically high mortality rate after major LEA serves as a call to action for clinicians, payers, and policy makers. Furthermore, the morbidity rate after LEA is also quite substantial, but it has been inadequately captured in studies. Arriving at a treatment strategy that leads to a reduction in LEA should be the goal of all clinicians caring for patients at risk for limb loss. Unfortunately, the recent American College of Cardiology (ACC)/American Heart Association (AHA) performance measures document for adults with PAD does not address patients at risk for or undergoing major LEA.[20] We therefore highlight several approaches that we think may lead to better patient outcomes.

Methods to reduce LEA

Improved recognition

The first step to reducing LEA is improved recognition of LE PAD by both patients and clinicians. Timing of presentation of patients with CLI significantly varies, with some presenting with rest pain and others ischemic ulceration or gangrene. The underlying reason for this poor recognition is the public's lack of awareness of the signs and symptoms of PAD.[11]

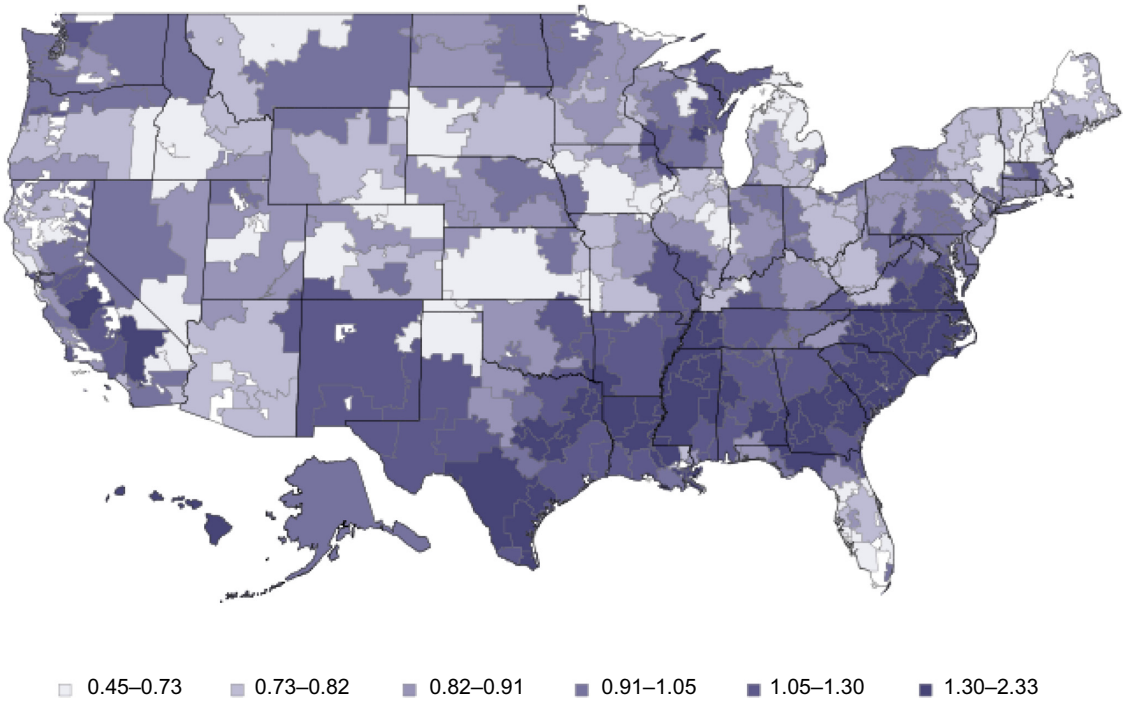

Figure 3 Geographic variation of major amputation of the lower extremity.
Note: The rates of major amputation of the lower extremity per hospital referral region (when normalized to the US) from inpatient Medicare data from 2000 to 2008.

In contrast, patient education of possible symptoms of MI is quite widespread in the US, in part due to the ACC/AHA practice guidelines and patient awareness campaigns that stress its importance.[21] Similar to treatment of MI, morbidity and mortality of CLI can be reduced significantly if patients are educated about prevention measures (eg, foot and toenail care) and the need to present for early evaluation if signs or symptoms arise. In response to studies that document lack of patient awareness, the national Peripheral Arterial Disease Coalition, an alliance of over 50 cardiovascular and vascular health professional societies, health advocacy groups, and government agencies, was founded to provide accurate health information to those with or at risk for PAD.

Encouragingly, there has been an overall decline in the rate of LEA from 7,258 per 100,000 patients with PAD in 2000 to 5,790 per 100,000 patients with PAD in 2008.[17] Possible explanations for the decreasing rate of LEA include improvements in screening and detection of vascular disease[16,22,23] and improvements in endovascular revascularization techniques and other treatments. Along with this decline in the rates of LEA, a concomitant decline in the all-cause mortality rate has also been observed.[15]

Advocacy for noninvasive and/or invasive imaging prior to LEA

Current decision making around the need for LEA and level of LEA is determined by physician expertise and preference. The threshold to perform LEA is different among various providers, and no uniform treatment algorithm exists. This may help explain some of the geographic variation in rates of LEA and mortality following LEA.[16,17] Significant regional differences exist in the intensity of diagnostic angiography, endovascular revascularization, and surgical revascularization in the year preceding LEA.[22] Another study found that among the 17,463 Medicare beneficiaries who underwent nontraumatic LEA from 2000 to 2010, only 68.4% underwent some type of arterial testing in the preceding 24 months.[24] Of these patients, 47.5% underwent ankle–brachial index measurement, 38.7% duplex ultrasound, 31.1% invasive angiography, 6.7% computed tomographic angiography, and 5.6% magnetic resonance angiography.[24] Women, younger patients, and patients living in rural areas were all less likely to receive preamputation arterial testing.[24]

A standardized approach to imaging prior to LEA may help reduce unnecessary limb loss and identify factors to help guide the decision regarding level of LEA. The NICE 2012 guidelines currently state not to perform major LEA in patients with CLI unless a vascular team has considered all options for revascularization,[15] but adherence to this guideline is not commonplace in the US. Furthermore, a consistent care pathway to determine the necessary level of major LEA is needed to preserve ambulatory status and decrease the occurrence of AKA due to extraordinarily high morbidity and mortality. Further research is essential in understanding "best practices" in imaging and preamputation testing prior to LEA.

Improved revascularization techniques

Significant advances in endovascular and surgical technology for PAD have occurred in the past decade, and, at least in the US, there has been a shift from surgical to endovascular revascularization.[25] When combined with improved screening and detection methods, the increased use of both surgical and endovascular revascularization in patients with PAD has likely contributed to the decline in LEA rates.[26] Examples of advances in endovascular technologies for revascularization that are being examined to improve outcomes in PAD include drug-coated balloons, atherectomy devices, chronic total occlusion recanalization devices, and improvements in stent technology.[27–32]

More research is necessary to determine the effects of endovascular versus surgical revascularization with regard to enhancing limb preservation. A recent meta-analysis of 23 trials comparing endovascular and surgical revascularization did not find any difference in mortality or LEA in approximately 12,800 patients with CLI.[33] The only randomized controlled trial included in this meta-analysis, the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) study, did not show a difference between endovascular and surgical revascularization.[34] However, this study enrolled patients over 10 years ago and did not allow endovascular stent placement in the angioplasty arm.

Novel therapies: cell therapy and gene therapy

Evidence-based treatments for atherosclerosis, such as antiplatelet agents, statins, and risk factor modification, are the mainstay of medical therapy for PAD. None of these therapies, however, directly affects LE blood flow. Over the past decade the use of biologic treatments to induce angiogenesis (ie, protein therapy, gene therapy, and cell therapy) has been investigated for treatment of advanced PAD.[35–40] Because of the short half-life of recombinant proteins, current clinical trials have approached the delivery of angiogenic factors through either a cell-based therapy or a gene therapy approach. Several phase II randomized, placebo-controlled

gene therapy trials have been promising, though a recent phase III trial of intramuscular nonviral 1 fibroblast growth factor compared with placebo did not demonstrate a reduction in LEA or death.[35,39,40] Despite this, therapeutic angiogenesis remains an intriguing option for the future because of a relative ease of administration and the potential to benefit from an autocrine/paracrine effect of the biologic substrates.

Gaps in evidence

There is a dearth of high-quality data available to aid clinical decision making in patients with CLI, a fact confirmed by a recent meta-analysis of 23 studies and the NICE guidelines.[15,41] The strength of evidence was rated low or insufficient for most findings in the observational trials. In addition to insufficient evidence to demonstrate a difference between the comparators, most of these studies did not assess functional outcomes, quality of life, or cardiovascular outcomes such as MI, stroke, or cardiovascular death. Furthermore, few studies measured the effect of treatment based on patient subgroups. Focusing on outcomes based on patient-specific factors such as presenting severity (eg, rest pain and tissue loss), comorbid conditions (eg, age, diabetes mellitus, and end-stage renal disease), and anatomic factors will help guide clinical decision making.

One of the biggest barriers to accumulation of knowledge in and across PAD therapies and technologies is the lack of consistent definitions and nomenclature across clinical trials. Additionally, recent clinical trials have used different outcomes, including surrogate end points such as procedural success and vessel patency. In response to the need to develop standard definitions and outcomes for LE PAD, PARC was formed. This group has broad representation from multiple disciplines in academia, industry, and regulatory agencies, and continues to work at accomplishing the aforementioned goals. Alternative data analytical methods, such as global rank end points, have also been proposed for use in trials rather than time to event models or objective performance goals.[42] This has the potential to more comprehensively evaluate the effect of a therapy, especially in early phase studies. It creates a hierarchy of end points based on clinical importance a priori, thus allowing for measures such as quality of life to be incorporated.[42]

Conclusion

An evolution in medical, endovascular, and surgical therapies aimed at improving PAD is underway. With the proliferation of revascularization devices and therapies, there is an increasing need for clarity regarding effectiveness data and the impact on amputations, mortality, MI, stroke, and quality of life. The recent announcement by the National Institutes of Health that funding has been approved for the Best Endovascular versus Best Surgical Therapy in Patients with Critical Limb Ischemia (BEST) trial (NCT02060630) is a positive step forward, but many more such steps need to be taken. The Patient Centered Outcomes Research Institute and the Institute of Medicine have both identified PAD as a health care priority. More studies that both identify outcomes that are important to patients and measure the effectiveness and safety of pharmaceuticals, biologic agents, and devices in patients at high risk for LEA are necessary.

Moving forward, clinicians and policy makers must continue to devise innovative ways to deliver high-value clinical care to patients with PAD. Although many have proposed quality improvement programs and even public reporting of CLI measures as ways to improve quality of care in PAD patients, a first step must be to better understand "best clinical practices" for patients at risk for CLI and with CLI. The possible unintended consequences of publicly reporting CLI measures and outcomes may be a shift toward the performing of fewer revascularization procedures, especially in the sickest patients who may benefit most from it. This has been observed in the use of primary PCI for ST segment elevation MI patients (ie, fewer revascularization procedures have been performed in regions/states that require public reporting of mortality after PCI).[43,44] Ultimately, our goal is to create a system to encourage necessary interventions for those PAD patients who would benefit from them the most.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Rooke TW, Hirsch AT, Misra S, et al. 2011 ACCF/AHA Focused Update of the Guideline for the Management of Patients with Peripheral Artery Disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2011;58(19):2020–2045.
2. Tendera M, Aboyans V, Bartelink ML, et al. ESC guidelines on the diagnosis and treatment of peripheral artery diseases: document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32(22):2851–2906.
3. Heald CL, Fowkes FG, Murray GD, Price JF. Risk of mortality and cardiovascular disease associated with the ankle-brachial index: systematic review. *Atherosclerosis*. 2006;189(1):61–69.
4. Subherwal S, Bhatt DL, Li S, et al. Polyvascular disease and long-term cardiovascular outcomes in older patients with non-ST-segment-elevation myocardial infarction. *Circ Cardiovasc Qual Outcomes*. 2012;5(4):541–549.
5. Andras A, Ferket B. Screening for peripheral arterial disease. *Cochrane Database Syst Rev*. 2014;4:CD010835.

6. Beckman JA, Jaff MR, Creager MA. The United States Preventive Services Task Force recommendation statement on screening for peripheral arterial disease: more harm than benefit? *Circulation*. 2006;114(8):861–866.
7. Hooi JD, Kester AD, Stoffers HE, Rinkens PE, Knottnerus JA, van Ree JW. Asymptomatic peripheral arterial occlusive disease predicted cardiovascular morbidity and mortality in a 7-year follow-up study. *J Clin Epidemiol*. 2004;57(3):294–300.
8. Twine CP, Coulston J, Shandall A, McLain AD. Angioplasty versus stenting for superficial femoral artery lesions. *Cochrane Database Syst Rev*. 2009;(2):CD006767.
9. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-society Consensus (TASC). *J Vasc Surg*. 2000;31(1 Pt 2):S1–S296.
10. Fowkes FG, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet*. 2013;382(9901):1329–1340.
11. Hirsch AT, Murphy TP, Lovell MB, et al. Gaps in public knowledge of peripheral arterial disease: the first national PAD public awareness survey. *Circulation*. 2007;116(18):2086–2094.
12. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients with Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-society Consensus; and Vascular Disease Foundation. *Circulation*. 2006;113(11):e463–e654.
13. Peacock JM, Keo HH, Duval S, et al. The incidence and health economic burden of ischemic amputation in Minnesota, 2005–2008. *Prev Chronic Dis*. 2011;8(6):A141.
14. Cruz CP, Eidt JF, Capps C, Kirtley L, Moursi MM. Major lower extremity amputations at a Veterans Affairs hospital. *Am J Surg*. 2003;186(5):449–454.
15. Layden J, Michaels J, Bermingham S, Higgins B. Guideline Development Group. Diagnosis and management of lower limb peripheral arterial disease: summary of NICE guidance. *BMJ*. 2012;345:e4947.
16. Jones WS, Patel MR, Dai D, et al. High mortality risks after major lower extremity amputation in Medicare patients with peripheral artery disease. *Am Heart J*. 2013;165(5):809–815.
17. Jones WS, Patel MR, Dai D, et al. Temporal trends and geographic variation of lower-extremity amputation in patients with peripheral artery disease: results from US Medicare 2000–2008. *J Am Coll Cardiol*. 2012;60(21):2230–2236.
18. Schanzer A, Mega J, Meadows J, Samson RH, Bandyk DF, Conte MS. Risk stratification in critical limb ischemia: derivation and validation of a model to predict amputation-free survival using multicenter surgical outcomes data. *J Vasc Surg*. 2008;48(6):1464–1471.
19. Goodney PP, Travis LL, Brooke BS, et al. Relationship between regional spending on vascular care and amputation rate. *JAMA Surg*. 2014;149(1):34–42.
20. Olin JW, Allie DE, Belkin M, et al. ACCF/AHA/ACR/SCAI/SIR/SVM/SVN/SVS 2010 performance measures for adults with peripheral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures, the American College of Radiology, the Society for Cardiac Angiography and Interventions, the Society for Interventional Radiology, the Society for Vascular Medicine, the Society for Vascular Nursing, and the Society for Vascular Surgery (Writing Committee to Develop Clinical Performance Measures for Peripheral Artery Disease). *J Vasc Nurs*. 2011;29(1):23–60.
21. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction – executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation*. 2004;110(5):588–636.
22. Goodney PP, Travis LL, Nallamothu BK, et al. Variation in the use of lower extremity vascular procedures for critical limb ischemia. *Circ Cardiovasc Qual Outcomes*. 2012;5(1):94–102.
23. Margolis DJ, Hoffstad O, Nafash J, et al. Location, location, location: geographic clustering of lower-extremity amputation among medicare beneficiaries with diabetes. *Diabetes Care*. 2011;34(11):2363–2367.
24. Vemulapalli S, Greiner MA, Jones WS, Patel MR, Hernandez AF, Curtis LH. Peripheral arterial testing before lower extremity amputation among Medicare beneficiaries, 2000 to 2010. *Circ Cardiovasc Qual Outcomes*. 2014;7(1):142–150.
25. Jaff MR, Cahill KE, Yu AP, Birnbaum HG, Engelhart LM. Clinical outcomes and medical care costs among medicare beneficiaries receiving therapy for peripheral arterial disease. *Ann Vasc Surg*. 2010;24(5):577–587.
26. Jude EB, Unsworth PF. Optimal treatment of infected diabetic foot ulcers. *Drugs Aging*. 2004;21(13):833–850.
27. Werk M, Langner S, Reinkensmeier B, et al. Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. *Circulation*. 2008;118(13):1358–1365.
28. Tepe G, Zeller T, Albrecht T, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. *NEJM*. 2008;358(7):689–699.
29. Stoner MC, deFreitas DJ, Phade SV, Parker FM, Bogey WM, Powell S. Mid-term results with laser atherectomy in the treatment of infrainguinal occlusive disease. *J Vasc Surg*. 2007;46(2):289–295.
30. Charalambous N, Schafer PJ, Trentmann J, et al. Percutaneous intraluminal recanalization of long, chronic superficial femoral and popliteal occlusions using the Frontrunner XP CTO device: a single-center experience. *Cardiovasc Intervent Radiol*. 2010;33(1):25–33.
31. Staniloae CS, Mody KP, Yadav SS, Han SY, Korabathina R. Endoluminal treatment of peripheral chronic total occlusions using the Crosser® recanalization catheter. *J Invas Cardiol*. 2011;23(9):359–362.
32. Pigott JP, Raja ML, Davis T. A multicenter experience evaluating chronic total occlusion crossing with the Wildcat catheter (the CONNECT study). *J Vasc Surg*. 2012;56(6):1615–1621.
33. Jones WS, Dolor RJ, Hasselblad V, et al. Comparative effectiveness of endovascular and surgical revascularization for patients with peripheral artery disease and critical limb ischemia: systematic review of revascularization in critical limb ischemia. *Am Heart J*. 2014;167(4):489–498.
34. Adam DJ, Beard JD, Cleveland T, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. *Lancet*. 2005;366(9501):1925–1934.
35. Belch J, Hiatt WR, Baumgartner I, et al. Effect of fibroblast growth factor NV1FGF on amputation and death: a randomised placebo-controlled trial of gene therapy in critical limb ischaemia. *Lancet*. 2011;377(9781):1929–1937.
36. Rajagopalan S, Mohler ER 3rd, Lederman RJ, et al. Regional angiogenesis with vascular endothelial growth factor in peripheral arterial disease: a phase II randomized, double-blind, controlled study of adenoviral delivery of vascular endothelial growth factor 121 in patients with disabling intermittent claudication. *Circulation*. 2003;108(16):1933–1938.
37. Morishita R, Aoki M, Hashiya N, et al. Safety evaluation of clinical gene therapy using hepatocyte growth factor to treat peripheral arterial disease. *Hypertension*. 2004;44(2):203–209.

38. Tateishi-Yuyama E, Matsubara H, Murohara T, et al. Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial. *Lancet*. 2002;360(9331):427–435.
39. Jones WS, Annex BH. Growth factors for therapeutic angiogenesis in peripheral arterial disease. *Curr Opin Cardiol*. 2007;22(5):458–463.
40. Powell RJ, Goodney P, Mendelsohn FO, Moen EK, Annex BH. Safety and efficacy of patient specific intramuscular injection of HGF plasmid gene therapy on limb perfusion and wound healing in patients with ischemic lower extremity ulceration: results of the HGF-0205 trial. *J Vasc Surg*. 2010;52(6):1525–1530.
41. Jones WS, Schmit KM, Vemulapalli S, et al. Treatment Strategies for Patients with Peripheral Artery Disease. Comparative Effectiveness Review No 118. (Prepared by the Duke Evidence-based Practice Center under Contract No 290–2007–10066-I.) AHRQ Publication No 13-EHC090-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2013.
42. Subherwal S, Anstrom KJ, Jones WS, et al. Use of alternative methodologies for evaluation of composite end points in trials of therapies for critical limb ischemia. *Am Heart J*. 2012;164(3):277–284.
43. Joynt KE, Blumenthal DM, Orav EJ, Resnic FS, Jha AK. Association of public reporting for percutaneous coronary intervention with utilization and outcomes among Medicare beneficiaries with acute myocardial infarction. *JAMA*. 2012;308(14):1460–1468.
44. Werner RM, Asch DA. The unintended consequences of publicly reporting quality information. *JAMA*. 2005;293(10):1239–1244.