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Outcomes for Clinical Studies Assessing Drug and Revascularization Therapies for Claudication and Critical Limb Ischemia in Peripheral Artery Disease

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Peripheral artery disease (PAD), which affects the large and medium arteries of the lower extremities, is a substantial cause of morbidity and health costs.[1–5] Clinical studies assessing treatments for PAD guide clinical management but require standard definitions of disease and outcomes to ensure validity and consistency within and between studies.

Prior guidelines for PAD outcomes in clinical trials were developed by consensus from stakeholders in multiple disciplines.[6–8] They consider outcomes of medical therapies targeting systemic atherosclerosis and medical or surgical therapies for leg-specific symptoms such as claudication or critical limb ischemia. However, the rapid development of percutaneous technologies and the promise of new biological therapies (eg, cell-based therapies) expand treatment options and require a re-evaluation of important outcomes in clinical trials of PAD.

Multidisciplinary consensus statements for other percutaneous treatments also provide insights to help develop standardized outcomes for trials of PAD. These include the Academic Research Consortium definitions for outcomes in percutaneous coronary interventions[9] and the Valve Academic Research Consortium definitions of outcomes for transcatheter aortic valve replacement.[10] Although this article is not meant to provide a definitive statement on outcomes for clinical trials on symptomatic PAD, it is designed to stimulate discussion toward a multidisciplinary consensus statement that embraces new percutaneous technologies and medical and surgical treatments for PAD.

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Definitions and Perspectives of PAD

PAD is defined clinically by an abnormal ankle-brachial index (ABI) ≤0.90.[6,7,11] The ABI for each leg is measured with a Doppler probe and is the ratio of the highest systolic pressure from the dorsalis pedis or posterior tibial artery in a leg divided by the highest arm systolic pressure.[11,12] Although there are other causes of PAD (eg, thromboembolic causes, inflammation, trauma, aneurysms, entrapment syndromes, adventitial cysts, congenital abnormalities),[12] atherosclerosis is the predominant cause of PAD. Medical therapy targeting risk factors for atherosclerosis reduces the risk of myocardial infarction and stroke, which are major causes of death in patients with PAD.[8,12–14] Thus, therapies designed to combat atherosclerosis in patients with PAD may focus on the prevention of wider clinical end points related to atherosclerosis such as myocardial infarction, stroke, and death, as well as leg-specific end points. Therapies designed specifically for leg-specific symptoms (medical therapy, cell-based therapy, or revascularization) may focus more on end points assessing these symptoms. Symptom impairment is also in the eye of the beholder. Patient perceptions may differ from health professionals' observations, and both provide information on the value of therapies for PAD.

Leg-Specific Symptoms in PAD

Although acute limb ischemia, characterized by the sudden loss of perfusion in a limb, may occur in PAD, a more chronic indolent form of leg ischemia is the most common symptomatic presentation of PAD and the focus of this discussion. Symptomatic chronic PAD manifests as claudication, defined as exertional discomfort related to exercise-induced ischemia of the lower extremities, or critical limb ischemia, defined by rest pain, skin ulceration, or gangrene.[8,12] Only ≈20% of patients with PAD have leg-specific symptoms of claudication or critical limb ischemia,[1–3,5] with up to another 50% having atypical leg symptoms that interfere with mobility.[3,15]

Leg-specific symptoms cause major morbidity by affecting pain-free mobility, functional performance, and quality of life.[16,17] These are less tangible end points than death, stroke, or myocardial infarction but are valued highly by patients with PAD. Clinical studies assessing the effects of drug and revascularization treatments on leg-specific symptoms or leg preservation in PAD typically differ in their primary end points. Some consensus is needed, particularly with the rapid development of new percutaneous therapies, because it will help comparisons of different modes of therapy between trials and facilitate comparative effectiveness studies.

Functional End Points

In 1999, the multidisciplinary Transatlantic Conference published guidelines for clinical trials in PAD recommending end points for medical therapies for claudication and surgical therapies for critical limb ischemia.[7] Since then, trials of medical therapy have used standardized measures of functional performance as primary end points such as walking times or distances measured by standardized treadmill protocols or a 6-minute corridor walk.[18–30] Studies of patients with critical limb ischemia using revascularization or angiogenesis trials focus on limb loss (amputation) and ulcer healing.[31–33] However, most

percutaneous revascularization trials[34–42] but not all[38,40–42] tend to focus on arterial patency and the need for repeat revascularization procedures. The inconsistency in outcomes between the various modes of treatment relates to the different treatment priorities in claudication compared with critical limb ischemia but may also reflect the different perspectives and priorities of those who manage PAD. It is not surprising that noninvasive clinicians who assess and treat PAD with exercise[43] gravitate to functional end points, whereas invasive clinicians and surgeons focus on end points more familiar to their clinical practice such as stenosis severity and repeat revascularization.

From the patient's perspective, the quality of life of claudicants centers on their discomfort during walking, whereas patients with critical limb ischemia are concerned with rest pain and the risk of limb amputation. Both claudication and amputation affect functional performance, independence in daily living, and thus quality of life. If function is the common goal in assessing limb-specific outcomes, how do anatomic end points and repeat revascularization help in assessing treatments for PAD?

Anatomic End Points

Anatomic end points such as degree of lumen narrowing and restenosis are arguably surrogate end points because they do not directly affect function but relate to mechanisms that might affect function. Arterial stenosis or occlusion may lower limb blood flow at rest and exercise and are key targets in revascularization strategies for claudication or critical limb ischemia. However, the relationship of restenosis or occlusion to symptoms and function after revascularization is poorly studied and likely to vary between individuals. In studies of PAD patients not receiving revascularization, ABI, a measure integrating the impact of all stenoses in a limb, is poorly associated with function.[44,45] Although measures of plaque burden correlate with walking distance,[46,47] improvement in function occurs with exercise training despite no change in ABI.[23,28,48] Other factors such as the development of collaterals and improvements in endothelial function and skeletal muscle bioenergetics may maintain function in the presence of arterial restenosis or occlusion.[43] Thus, improving blood flow by revascularization usually has a major effect on symptoms and tissue healing, but the degree of restenosis reflects only 1 parameter related to the durability of these outcomes.

Revascularization trials often use noninvasive duplex ultrasound or invasive angiography to identify stenoses of >50% narrowing compared with a reference segment.[32,34,37–40,42,49,50] However, the physiological significance of a stenosis depends on stenosis severity, lesion length, and irregularity, all of which contribute to energy loss and decreased pressure and flow beyond a stenosis. Although these factors are captured in discrete lesions by duplex ultrasound, these parameters are deceptive and difficult to assess in long or serial lesions and by noninvasive (eg, magnetic resonance or computerized tomography angiography) and invasive angiography. A major limitation of all imaging modalities is that they assess stenoses at rest, which is incongruous with the physiology of claudication, that is, a symptom occurring with activity, higher blood flow rates, and potentially different vasomotor tone compared with the resting state.

Arterial stenosis defined by imaging is a powerful incentive for revascularization. In clinical trials of percutaneous coronary interventions, subgroups with anatomic restenosis defined by routine angiography had higher rates of repeat revascularization than subjects followed up clinically without imaging.[51,52] Thus, identifying anatomic restenosis (typically >50%) is in itself a potent driver of repeat revascularization and overestimates the clinical failure rate of coronary stenting. There is every reason to expect that routine duplex ultrasound or angiography will also overestimate the need for repeat revascularization in PAD trials. Most duplex criteria for restenosis in PAD trials identify a >50% stenosis and were developed from comparisons with angiography after femoral revascularization.[53–55] Although a >50% stenosis defines an anatomic "failure" of revascularization therapy, the relationship of >50% stenosis to clinically important outcomes (recurrent claudication, delayed healing, or arterial occlusion or thrombosis) is poorly described. This could partially explain why restenosis or failed patency defined by anatomic parameters sometimes diverges from self-reported or measured functional assessments of walking in revascularization trials.[49,50]

Some investigators advocate screening for stent fracture during follow-up because it is associated with restenosis. However, this reflects device durability and a potential mechanism of restenosis, which may affect device clearance by regulatory bodies. Arguably any clinically important adverse effect of stent fracture will be captured by symptom recurrence, reduced walking function, or need for revascularization.

Anatomic end points that do not reflect current treatment practices are also difficult to interpret. For example, technical failure of balloon angioplasty at the initial procedure defined by anatomic criteria (eg, abrupt closure, flow-limiting dissection, or severe recoil of an artery with a residual significant stenosis) would usually be treated by bailout stenting and would not contribute to the final end point of a clinical trial. This was the approach used in the original coronary stent trials.[56,57] In several recent PAD trials comparing stents and angioplasty, bailout stenting was considered a treatment failure and counted as the primary end point.[49,50] Including bailout stenting as a primary end point substantially inflated the end points in the angioplasty group, favoring the new stent design.[58,59] This approach makes little sense because bailout stenting is considered part of the strategy for balloon angioplasty,[56,57] and its pathology (abrupt closure, dissection, recoil) is very different from restenosis and thrombosis, which drives later stent and graft failure.[59] The rate of bailout stenting varies widely among different studies. In 2 earlier PAD stent trials,[38,41] bailout stenting was 11% to 80% lower, respectively, than in recent trials, suggesting that bailout stenting is determined by the criteria governing its use in clinical trials and variability in their interpretation.

Randomized Versus Historical Control Trial Designs

Despite the prevalence of PAD, randomized trials of therapies in PAD paradoxically take a long time to recruit subjects and are difficult to complete, perhaps because of the "unfounded belief of lack of clinical equipoise between randomized treatments that bias physicians and patients."[60] Although the Food and Drug Administration permits device evaluation by singlearm comparisons with historical controls in specified situations (eg,

prosthetic heart valves),[61] this is an unsatisfactory solution to PAD therapies in which lack of standardization across trials is the rule, particularly for percutaneous treatments.

Furthermore, the objective of device clearance by regulatory bodies such as the Food and Drug Administration by meeting minimum performance criteria is different from evaluating whether a strategy offers clinical benefit beyond usual care or other devices. Although some groups support singlearm studies against optimal performance criteria, particularly for PAD device-based therapies,[62,63] they may provide an air of legitimacy that could bias providers and impede the completion of randomized trials assessing their efficacy compared with standard treatment.

Randomized trials demonstrate successful treatment options in PAD and identify treatments that offer no benefit and would otherwise squander our limited medical resources.[25–27] Improving the efficiency of study enrollment and completion requires us to acknowledge the uncertainty and equipoise in many of our novel drug and device treatments. A controversial incentive to this approach includes delaying reimbursement until randomized trials demonstrate efficacy, an approach used to encourage enrollment in trials of carotid stenting in the United States.[64]

Efficacy and Safety

The Transatlantic Conference on Clinical Trial Guidelines published in 1999 strongly favored randomized, controlled trials and functional outcomes as primary end points for assessing medical treatment of PAD symptoms.[7] These include treadmill testing to assess claudication time or distance for trials of patients with claudication. More recently, some studies suggest that other less challenging functional tests such as the 6-minute or 4-m walk tests may be better primary end points for elderly or infirm subjects in claudication trials.[65] In patients with PAD, these alternative end points are related to mortality and cardiovascular events,[66,67] as are abnormal walking times on treadmill testing.[68] Additional assessment of quality of life adds a patient perspective to the evaluation of treatment and complements the observational data on function. The central role of functional assessments and quality of life is to integrate the effects of restenosis, repeat revascularization, and other factors that could be secondary end points in claudication trials.

In trials of critical limb ischemia, the Transatlantic Conference on Clinical Trial Guidelines supported primary end points of complete resolution of rest pain, complete ulcer healing, and avoidance of major amputation.[7] However, doubts about the objectivity of measuring pain at rest and partial ulcer healing limit the validity of these end points.[62] Because cardiovascular end points are particularly high in patients with critical limb ischemia, they are often considered in composite primary or secondary end points for critical limb ischemia.[7]

Over the last decade, percutaneous revascularization has increasingly been a major treatment option for symptomatic PAD, but the principles of these guidelines are not always used in clinical trials. Other device-related guidelines for coronary interventions (Academic Research Consortium)[9] and percutaneous heart valves (Valve Academic Research Consortium)[10] suggest that end points should relate to the pathophysiological mechanisms

most likely responsible for the clinical outcome and represent essential patient-orientated clinical outcomes.[9,10] Safety end points concern avoidance of short-term device-related or procedural complications[9,10] and longer-term adverse outcomes regardless of whether they are specifically related to the device.[9]

These device-based recommendations could guide similar consensus statements for end points and trial design for percutaneous treatments of PAD and expand on current guidelines.[7] Functional end points should be primary measures of efficacy in clinical trials and include walking performance in claudication (eg, peak walking time or 6-minute walking distance) and preservation of the limb (avoiding major amputation) in critical limb ischemia. Safety end points should capture adverse events of treatment and may differ according to the treatment. For example, in all treatments, death, myocardial infarction, and stroke may be considered. In revascularization trials, repeat revascularization reflects potentially avoidable use of medical resources, and major amputation may be a safety end point in claudication trials (as opposed to an efficacy end point in trials of critical limb ischemia).

Suggested Efficacy End Points in Clinical Studies of PAD

End Points Assessing Walking Function

Measures of walking endurance include peak walking time (also called maximum or absolute walking distance) and claudication onset time (also called pain-free, initial, or ischemic claudication distance) from standardized treadmill tests and the distance covered in a standardized 6-minute walk test.[7,69–71] Walking speed may be assessed by the 4-m walking velocity test, and tests of balance and repeated chair rises are examples of assessments of strength and coordination related to mobility.[65,72]

PAD treadmill testing uses less vigorous protocols than coronary stress testing (eg, the Gardner protocol[71]; Table 1) and is used commonly in clinical trials of medical therapy for claudication. Compared with constant-load protocols, graded treadmill tests start with a lower workload to accommodate highly limited patients and progress to higher workloads to challenge subjects with higher activity levels and to avoid the walk-through phenomenon.[7] The claudication onset time refers to the time at which claudication is first experienced by the subject. The peak walking time is the time when the subject cannot walk further because of symptoms. These times are sometimes converted to distances based on the constant speed of the treadmill. However, this ignores the progressive increase in workload in graded treadmill protocols in which the gradient increases at set time intervals. The peak walking time is more reproducible than the claudication onset time with graded protocols.[69,70]

Corridor-based tests include the 6-minute walk test, which measures walking endurance using a standard protocol in which subjects walk up and down a 100-ft hallway for 6 minutes after being told to walk as long as possible.[65] The end point is the distance walked over 6 minutes. It is reproducible in patients with PAD[65] and is considered less challenging for older infirm subjects. The 4-m walking velocity test measures the fastest walking velocity over 4 m after subjects are asked to walk the distance at their usual pace and at their fastest pace.[65] The Short Physical Performance Battery is a score combining the results of

the 4-m walking velocity, time to rise from a seated position 5 times, and standing balance.[65,72] Thus, it measures other aspects of mobility such as balance in addition to walking performance.

Each of these tests requires subject familiarization and standardization in multicenter studies to avoid increased variability across sites.[73] The choice of primary end point depends on the study population. Although standardized treadmill tests are common and provide the greatest ability to compare different interventions and studies, they may cause anxiety or injury in older or more infirm subjects. Thus, in more infirm populations, other measures of walking function such as the 6-minute walk test may be a more appropriate primary end point. A training effect is potentially important in trials in which exercise regimens using a treadmill are offered to 1 treatment arm only (eg, the Claudication: Exercise Versus Endoluminal Revascularization [CLEVER] trial).[30] This could potentially overestimate the benefits of exercise if the primary end point is measured by treadmill rather than one of the other tests of walking function.

Quality-of-Life Questionnaires

Whereas tests of walking function provide objective measures by an observer, quality-of-life questionnaires assess the subject's perception of his or her own walking ability and the overall impact of disease on the subject's emotional and social well-being. This subject-orientated view provides additional information, and quality-of-life questionnaires were widely used in earlier studies of PAD.[16] Questionnaires are either general tools used in a variety of diseases (eg, Short Form-36, European Quality of Life Questionnaire) or PAD-specific questionnaires (eg, Walking Impairment Questionnaire, Peripheral Artery Questionnaire) and are reviewed in detail elsewhere.[16] Changes in quality-of-life scores as a result of successful PAD therapies relate to changes in measures of walking function (eg, treadmill walking distance) in many trials[16,19,24,74–76] but are divergent in others,[30] suggesting that quality-of-life scores measure dimensions of PAD not always captured by functional measures.

Quality-of-life questionnaires are relatively cheap to administer and interpret compared with other end points but require the completion of all items on the questionnaire.[73] None of the PAD questionnaires are accepted by the Food and Drug Administration as patient outcomes for regulatory purposes. Thus, they are important secondary end points in clinical studies.

Anatomic End Points

Patency of an artery or graft refers to the lack of restenosis or need for revascularization. Revascularization may reflect restenosis of a target lesion or disease progression causing a new lesion in an artery or graft. Patency has its roots in the surgical literature when this was the main mode or revascularization. Primary patency refers to "uninterrupted patency" in which no procedure (eg, angioplasty or graft revision) is required within a graft or its 2 anastomoses over a specified length of follow-up.[77] Assisted primary patency refers to the patency of a graft over time, which may include a procedure to correct an abnormality (eg, stenosis) in an open graft, whereas secondary patency refers to the patency of a graft over time, which includes a procedure to restore flow in an occluded graft.[77] This terminology

extended into the percutaneous literature, with the additional definition of a >50% stenosis in an intervened artery as failed patency.[63] As described earlier, the legitimacy of this latter definition is questionable because it is an imperfect predictor of function, artery or graft occlusion, or need for reintervention.

Duplex ultrasound is attractive as an end point to assess patency because it is noninvasive. Segments of an artery or graft are interrogated by pulsed Doppler to derive peak systolic velocities ratios from within a stenosis to the immediate proximal nonstenosed reference segment. Different validation studies report a wide range of duplex ultrasound velocity ratios (1.5–2.5), corresponding to an angiographic lumen stenosis of >50%.[53,55,78–80] These are derived from studies of native disease,[55,79] post--balloon angioplasty disease,[80] and poststent disease[53,78] and often from symptomatic subgroups. Different ratios are used in different trials, but the relevance of these criteria to the recurrence of symptoms or risk of thrombosis is less clear.[81,82] The only randomized trial to assess the value of duplex ultrasound surveillance and a peak systolic ratio >2.0 in patients receiving bypass grafts for PAD showed no effect on graft patency.[83] Thus, the specific duplex criteria that relate to a clinically important outcome such as recurrent symptoms or clinically determined repeat revascularization are uncertain. Restenosis provides insight into one potential mechanism of decreased function with a therapy. Thus, it is arguably a better secondary end point in PAD revascularization trials.

Repeat Revascularization

Repeat peripheral revascularization is an important end point after initial percutaneous or surgical revascularization because it exposes patients to additional procedural risks and discomfort and reflects a further use of medical resources (ie, an economic impact).

Surgical guidelines define major revascularization (new surgical bypass graft, use of thrombectomy or thrombolysis, or major surgical revision such as an interposition or jump graft) or minor revascularization (balloon angioplasty, ather-ectomy, stenting).[62] In an extension of the coronary literature,[9] target lesion revascularization (any repeat percutaneous revascularization to the target lesion or bypass surgery to the target vessel) and target vessel revascularization (any revascularization to any segment of the target vessel) are common end points in percutaneous peripheral revascularization trials.[49,50]

A key issue with repeat revascularization is whether it is influenced by symptoms or by imaging (duplex ultrasound or angiography). Coronary guidelines recommend ascertainment of the need for revascularization before routine imaging in trials,[9] and similar guidelines are prudent PAD trial protocols.[9,62] Clear guidelines for bailout stenting for patients allocated to balloon angioplasty should be described in trial protocols and not included as primary end points.

Physiological End Points

The ABI usually changes little, if at all, with medical and physical therapies that improve claudication symptoms.[69] However, the ABI should improve with percutaneous or surgical revascularization and is an objective measure of the resting gradient in the large and medium arteries as a result of atherosclerosis. The ABI can be normal or nearly normal in very

proximal disease, and the exercise ABI is a more sensitive measure of the physiological significance of obstructive disease with maximal or exercise-induced blood flow.[84] The intraindividual variability of ABI measurement is ≈0.10 to 0.15,[8] and changes greater than this are often used to indicate a clinically significant change. Because past definitions of ABI have varied across studies, trials should use a standard approach (using the highest pedal pressure rather than the mean pedal pressure)[8,11] and avoid other factors that may increase the variability and lower power to find differences in studies.[73]

Classification of Critical Limb Ischemia

The Rutherford classification, commonly used in North America, has 7 categories of PAD, ranging from asymptomatic PAD to claudication and critical limb ischemia with ulceration or gangrene (Table 2).[8] The Fontaine classification, commonly used in Europe, has 5 categories (Table 2), which correspond to Rutherford categories.[8] Critical limb ischemia is defined as Fontaine III to IV or Rutherford 4 to 6 categories. Although patients with critical limb ischemia have low limb pressures (eg, <50-mm Hg ankle pressure or <30-mm Hg toe pressure),[8] these cut points or cut points defined by ABI have varying sensitivity and specificity and limit their value as definitions of critical limb ischemia.[7] However, ABIs are often described in trials of critical limb ischemia and are useful for comparing baseline characteristics between studies and average changes in perfusion with revascularization.

Amputation

When amputation is required in critical limb ischemia, conventional surgical practice aims for the lowest level of amputation that will heal.[8] Minor amputations of the toes or toe rays or at the transmetatarsal level generally do not impair walking function and do not require prostheses for the patient to walk.[77] Often considered limb salvage operations,[8] they are usually not considered in primary end points in trials of critical limb ischemia. However, past guidelines propose that major amputations (defined as at the ankle or above)[7,8,77] can be included as primary end points. Because criteria for amputation and choosing the level of amputation vary, prior guidelines recommend that criteria for amputation be clearly defined in the study protocol.[7]

Wound Healing and Pain Relief

Wound healing and relief of rest pain are important end points from the patient's viewpoint but are subject to observer variability and informative censoring. For example, censoring subjects receiving amputation may overestimate the benefit of a therapy on wound healing. In this case, amputation is a competing risk for wound healing and potentially a marker for poor wound healing. Complete wound healing and complete relief of pain (without the use of analgesics) are less subject to observer variation than partial changes in these end points and are recommended measures for these secondary end points in prior guidelines.[7]

Survival and Cardiovascular Events

Studies with interventions designed to target cardiovascular disease and death in patients with PAD often use composite end points consisting of the first event of cardiovascular death, myocardial infarction, stroke, amputation, and coronary or peripheral

revascularization.[7] These may constitute the primary efficacy end point in prevention studies but could be short-term procedural or operative safety end points in revascularization studies or long-term safety end points in all studies.

Suggested Safety End Points in Studies of PAD

Composite safety end points include adverse effects specific to the treatment, short-term risks of revascularization procedures or operations, and long-term outcomes related to limb symptoms, limb survival, nonfatal cardiovascular events, or death. Prior guidelines for peripheral and coronary percutaneous or surgical revascularization trials define short-term risks as those occurring within 30 days of the procedure/operation).[9,62,77] These aim to capture procedure/ operation-related adverse events and include the composite of death, cardiovascular events, and major amputation.[7,62] Trials of angiogenesis have also included potential off-target responses to growth factors, including malignancy, retinopathy (neovascularization), edema, hypotension, and proteinuria[18]

Long-term Efficacy End Points for Clinical Trials of Claudication at 1 Year

Tables 3 and 4 suggest long-term clinical outcomes for clinical trials of PAD. They are based on previously published recommendations for trials of medical and revascularization therapies for PAD and trials of percutaneous coronary and valve procedures.[7–9,62,77] Table 5 provides a summary of the tools used to obtain outcomes in PAD with suggestions for the types of trials that may suit the outcome.

Conclusions

Clinical trials of therapies for PAD are required to tackle the high morbidity and cost of this disease. In many cases, the outcomes used in clinical trials, particularly of percutaneous therapies, do not reflect the major concern of function and symptoms in patients. Older guidelines of medical and surgical therapies provide a path to develop more inclusive guidelines that are patient-oriented and provide greater standardization of outcomes across trials to permit comparisons between different therapies. The proposals presented here could form a foundation for discussion and agreement among important stakeholders such as patient groups, professional societies, government representatives (eg, the Centers for Medicaid and Medicare Services and the Food and Drug Administration), and industry.

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Table 1

The Gardner Graded Exercise Treadmill Protocol for PAD

Time, min	Speed, mph	Grade, %
0	2.0	0
2	2.0	2
4	2.0	4
6	2.0	6
8	2.0	8
10	2.0	10
12	2.0	12
14	2.0	14
16	2.0	16

PAD indicates peripheral artery disease. In the Gardner protocol, the speed is a constant 2.0 mph, with an increase in gradient of 2% every 2 minutes.[71] The Hiatt graded protocol uses a similar concept with a constant speed of 2.0 mph and an increase in gradient of 3.5% every 3 minutes.[69]

Table 2

Rutherford Categories and Fontaine Stages of PAD

PAD Classification	Clinical Symptom	Rutherford	Fontaine
Asymptomatic	Asymptomatic	0	I
Intermittent claudication	Mild claudication	1	IIa
	Moderate claudication	2	IIb
	Severe claudication	3	IIb
Critical limb ischemia	Ischemic rest pain	4	III
	Minor tissue loss	5	IV
	Ulceration or gangrene	6	IV

PAD indicates peripheral artery disease.

Table 3

Potential Characteristics of Trials Assessing PAD Symptoms (Not Cardiovascular Morbidity/Mortality)

	Intermittent Claudication		Critical Limb Ischemia	
	Medical Therapies	**Revascularization Therapies**	**Medical Therapies**	**Revascularization Therapies**
Patient selection	Intermittent claudication for >6 mo and ABI <0.9	Intermittent claudication for > 6 mo and ABI <0.9	Pain at rest or ulceration/ gangrene of the foot or toes and Ankle pressure ≤50 –70 mm Hg or toe pressure ≤30 –50 mm Hg	Pain at rest or ulceration/ gangrene of the foot or toes and Ankle pressure ≤50 –70 mm Hg or toe pressure ≤30 –50 mm Hg
Trial design	RCT double-blind	RCT with at least blinded end-point assessment	RCT double-blind	RCT with at least blinded end-point assessment
Duration	6 mo–1 y	1–2 y	6 mo–1 y	1–2 y
Primary efficacy end point	Peak walking time*	Peak walking time*	Major amputation±death, MI, CVA	Major amputation±death, MI, CVA
Secondary end points	Claudication onset time	Claudication onset time	Complete ulcer healing	Complete ulcer healing
	6-min walk	6-min walk	Pain relief	Pain relief
	Quality of life	Quality of life	Quality of life	Quality of life

ABI indicates ankle-brachial index; CVA, cerebrovascular accident; MI, myocardial infarction; PAD, peripheral artery disease; and RCT, randomized, controlled trial. Medical therapies include pharmacological or cell-based therapies; revascularization includes open surgical or percutaneous methods.

*The 6-minute walking distance may be a more appropriate primary end point than peak walking time if the subject group is frail or if exercise therapy with a treadmill is in 1 arm of a trial and could lead to a learning/training effect.

Table 4

Potential Characteristics of Safety End Points in Trials Assessing PAD Symptoms

	Intermittent Claudication		Critical Limb Ischemia	
	Medical Therapies	**Revascularization Therapies**	**Medical Therapies**	**Revascularization Therapies**
Duration	Duration of trial	1. Related to operation/device within 30 d and 2. duration of trial	Duration of trial	1. Related to operation/device within 30 d and 2. duration of trial
All-cause mortality	Considered more unbiased but potentially less specific than cause-specific death			
Cardiovascular mortality	Cardiac, cerebrovascular, or vascular death or when unequivocal noncardiovascular death cannot be established; assessment blinded to treatment allocation			
Myocardial infarction	Troponin or CK above the upper limit of reference range (99th percentile) and symptoms or ECG changes or loss of viable myocardium or pathological findings at autopsy[85]			
TVR or TLR	Defined by symptoms and a decrease in ABI >0.15[8] or functional walking test; assessment blinded to treatment allocation before imaging, *followed by* demonstration of physiologically significant restenosis by imaging/pressure gradient			
Major bleed	Life-threatening bleed (fatal, into a critical organ, or associated with shock or drop in hemoglobin of >5g/dL) or major bleed (overt bleeding with drop in hemoglobin >3.0 g/dL)[10]			
Acute kidney injury	Modified RIFLE[10]			

ABI indicates ankle-brachial index; CK, creatine kinase; PAD, peripheral artery disease; RIFLE, risk, injury, failure, loss, and end-stage kidney disease; TLR, target lesion revascularization; and TVR, target vessel revascularization. Medical therapies include pharmacological or cell-based therapies; revascularization includes open surgical or percutaneous methods.

Table 5

Tools Used to Measure Outcomes in PAD, and Examples of Trial Designs That Could Use These as Primary or Secondary Outcomes

Outcome Category	Tool	Outcome Variable	Potential Trial
Function/observer measures	Graded exercise treadmill	Time(peak walk time and claudication onset time)	Trials in claudication using drugs,[26,29] revascularization, cell-based therapies, or exercise[24,30]*
	6-min walk	Meters	Trials in claudication using drugs, revascularization, cell-based therapies, or exercise,[19] especially in frail populations
	4-m walk	Meters per second	Trials in claudication using drugs, revascularization, cell-based therapies, or exercise, especially in frail populations
Function/subject perception	Quality of life(by domains or total score)	Unit score	Trials in claudication or critical limb ischemia using drugs,[29,75] revascularization,[49] cell-based therapies, or exercise[20,30]
Clinical	Death/myocardial infarction/stroke	Absolute incidence and hazard ratio (vs comparison treatment using survival analysis)	Trials in claudication (safety) or critical limb ischemia using drugs,[26] revascularization,[31,38,41,49,50] cell-based therapies, or exercise
	Clinically driven repeat revascularization† (target lesion/ vessel revascularization)	Absolute incidence and hazard ratio (vs comparison group using survival analysis)	Trials in claudication or critical limb ischemia using revascularization (percutaneous or open surgery)
	Major amputation†	Absolute incidence and hazard ratio (vs comparison group using survival analysis)	Trials in claudication (safety) or critical limb ischemia using drugs, revascularization,[31,38,41,49,50] cell-based therapies, or exercise
Anatomic	Restenosis/graft occlusion	Angiography: percent stenosis vs reference segment	Mechanistic end point in trials in claudication or critical limb ischemia using drugs[86] or revascularization (percutaneous[38,41,49,50] or open surgery)[31]
		Duplex ultrasound: percent stenosis based on ratio of PSV in lesion to PSV in proximal reference segment	

PAD indicates peripheral artery disease; and PSV, peak systolic velocity. It is unclear what angiographic restenosis or PSV ratio reflects a clinically important measure f restenosis. References are examples of studies using these outcomes.

*Treadmill tests may be biased by a learning effect if the intervention is treadmill-based exercise and offered only to 1 treatment group.

†Revascularization defined by clinical or functional criteria (not imaging) and major amputation determined by prospective criteria.