

STATE-OF-THE-ART REVIEW

Objective Outcome Measures for Trials in Patients With Chronic Limb-Threatening Ischemia Across 2 Decades



Analysis and Recommendations

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ABSTRACT

Chronic limb-threatening ischemia (CLTI) is prevalent and associated with morbidity and mortality. The published research concerning CLTI therapeutics is evolving. The goals of this review are to: 1) summarize the endpoints that are being used in trials assessing interventions for patients with CLTI; and 2) review gaps and discrepancies in current outcome definitions. A search was conducted of the PubMed database and ClinicalTrials.gov to identify studies published between January 2000 and March 2020 that evaluated treatment options for patients with CLTI. Meta-analyses, case series, case reports, abstracts, and expert opinion were excluded. Forty-nine studies (n = 11,667) were identified that fulfilled the inclusion criteria. Most trials reported clinical outcomes (mortality, 69.4%; limb events, 87.8%; target lesion revascularization, 83.7%). Mean follow-up duration was 23.7 months. In investigational device exemption trials, total follow-up and follow-up to primary outcomes were discordant (12 months vs 6 months; $P = 0.0018$). Hemodynamic testing was reported in 71.4%, usually ankle-brachial index. Patency was assessed in 89.8% of trials; ultrasound was used in 65.3% and invasive angiography in 85.7%, at baseline and/or during follow-up. Wound assessment was performed in 49.0% of studies, qualitative in 28.6% and quantitative in 20.4%. Finally, quality of life assessment was performed in 55% of studies. Definitions for many outcomes varied across studies. Consensus regarding which outcomes to study, uniform definitions, and optimal methods to measure some of these outcomes are yet to be established. A comprehensive effort by all stakeholders is needed to move the field of CLTI forward.

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HIGHLIGHTS

- Variability in CLTI trial outcomes hinders the study of this devastating condition.
- A core group of outcomes should be assessed in every CLTI trial.
- A coordinated multistakeholder effort is needed to advance the field of CLTI.

Chronic limb-threatening ischemia (CLTI), also referred to as critical limb ischemia, is the most severe form of peripheral artery disease (PAD) (1). Clinically, CLTI is defined as rest pain, nonhealing ulceration, or gangrene of the lower extremity. Anatomically, CLTI may result from multi-level PAD and/or from below-the-knee occlusive disease.

The evidence base for CLTI therapies has been slow to evolve because of the distinct challenges this population poses to study design and execution. Generating high-quality evidence through randomized clinical trials of novel interventional therapies for CLTI has proved time consuming and costly. In addition, patients with CLTI often have complex medical comorbidities that are commonly compounded by socioeconomic difficulties and diminished life expectancy. As a result, the published research to date is composed predominantly of small observational studies, low-quality retrospective analyses, and limited cohort industry-sponsored device trials for the evaluation of novel devices.

OUTCOME CHOICE AND IMPLEMENTATION IN CLTI TRIALS: DEFINING THE PROBLEM

The study of lower extremity revascularization in PAD has been maturing for more than 2 decades (2); however, most studies have focused on medical devices intended for patients with intermittent claudication. These trials have been reporting efficacy-related endpoints, such as primary patency and clinically driven target lesion revascularization (TLR), as well as safety outcomes such as mortality and amputation rate, among others. Although similar outcomes are tracked in CLTI trials, factors that influence these outcomes may be only partially affected by the studied intervention. For instance, wound healing is not exclusively dependent on arterial perfusion, and mortality is more commonly attributed to coexistent cardiac and cerebrovascular atherosclerosis than the success or failure of the studied CLTI interventions (3).

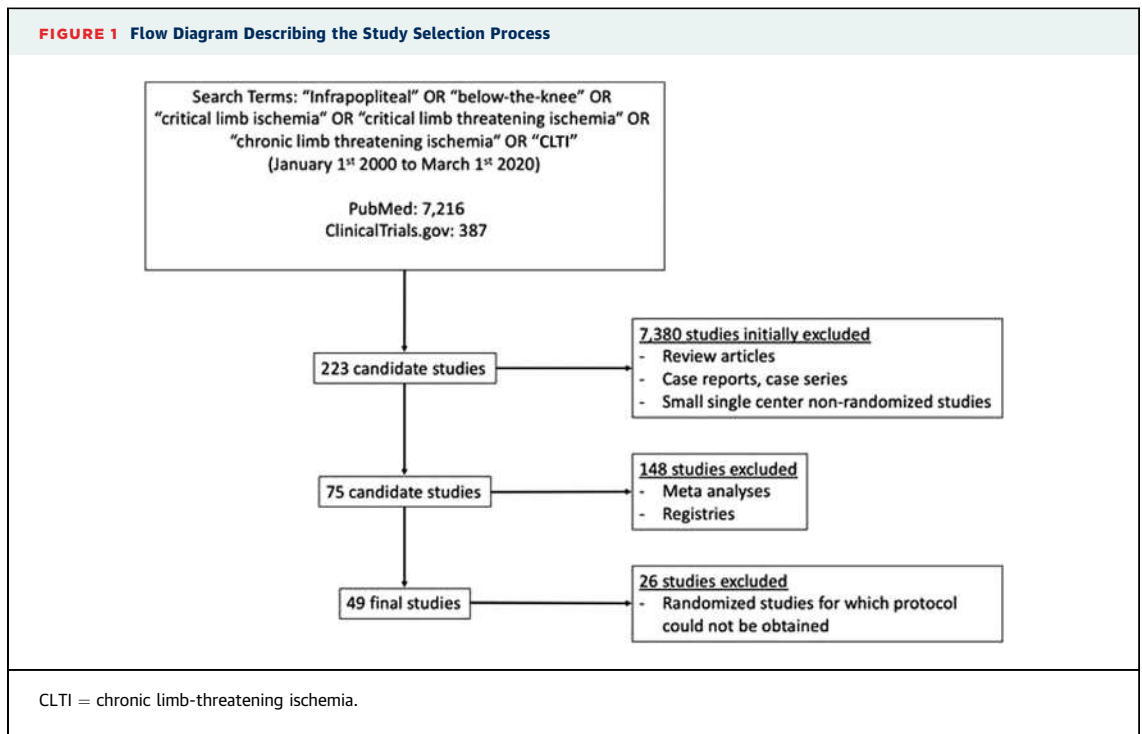
Thus, many of the established endpoints for PAD trials that were developed primarily for patients with claudication may be poorly suited for CLTI trials. First, the purpose of revascularization in CLTI is different than it is for patients presenting with intermittent claudication. The goal for a patient with claudication is long-lasting improved walking while minimizing subsequent interventions. Limb salvage is the principal goal of revascularization for patients with CLTI, and once wound healing has occurred, primary patency becomes less of an issue. Indeed, many patients and physicians may be receptive to secondary endovascular interventions for limb salvage when needed. Thus, although long-term primary patency is desirable, it is not the sole measure of an

intervention's value to patients with CLTI (eg, a short-term goal might be to improve blood flow and establish patency, while a long-term goal might be limb salvage through primary and secondary patency). Second, the natural history of PAD in a patient with intermittent claudication is different from that of a patient with CLTI, leading to different tolerance for adverse events and repeat interventions (4,5). For example, major amputation will be considered catastrophic after a procedure in a patient with claudication but may not be avoidable in a substantial minority of patients with CLTI in today's practice. Finally, some outcomes are entirely different between claudication and CLTI. For example, how to define wound healing (eg, rate of healing vs complete closure) is relevant only to patients with CLTI.

There have been attempts to standardize CLTI trial reporting. The Society for Vascular Surgery Critical Limb Ischemia Working Group established a variety of standardized objective outcomes that were derived from open bypass randomized controlled trials to create a benchmark for CLTI therapies (6,7). The 3 central outcomes established by this work group were major adverse limb events (MALE), post-operative death (POD), and amputation-free survival (AFS). The group recommended using MALE plus POD as the primary efficacy endpoint, complemented by AFS as a secondary endpoint. In an early attempt to promote the use of "patient-centric" outcomes measures, the group also recommended the collection of data that would illuminate the overall burden of reintervention over the course of follow-up. Nonetheless, these early attempts may not be entirely relevant to current trials. For example, the definition of MALE established by this group included the need for open surgery,

ABBREVIATIONS AND ACRONYMS

- ABI** = ankle-brachial index
- AFS** = amputation-free survival
- CLTI** = chronic limb-threatening ischemia
- DUS** = duplex ultrasonography
- IDE** = investigational device exemption
- MALE** = major adverse limb event(s)
- PAD** = peripheral artery disease
- POD** = postoperative death
- QOL** = quality of life
- TBI** = toe-brachial index
- TLR** = target lesion revascularization



which is uncommon in modern practice in the early period after endovascular intervention.

Nonetheless, in practice, there is much variation in selecting outcomes for CLTI trials, in outcome definitions, and in how these outcomes are reported (Supplemental Tables 1 and 2). Indeed, calls to improve CLTI-related trial design are abundant (8).

The goals of the present review are: 1) to summarize the endpoints that are currently being used in trials assessing interventions for patients with CLTI; and 2) to review gaps and discrepancies in current definitions of outcomes. Of note, the purpose of this review is not to evaluate the results of the selected studies.

METHODS

We conducted a comprehensive search of the PubMed database and ClinicalTrials.gov to identify studies published between January 2000 and March 2020 that evaluated treatment options for patients with CLTI. We used the following search terms: 1) “below-the-knee” or “infrapopliteal” or “critical limb ischemia”; 2) “CLTI” or “chronic limb threatening ischemia” or “critical limb threatening ischemia”; and 3) “CLTI” and “chronic limb threatening ischemia” and “critical limb threatening ischemia.” Any trials that were not identified by these methods but were known through other means, such as coauthor

personal communications or core laboratory records, were also included.

Studies were reviewed by 3 coauthors (R.D., S.M., and V.L.). Studies that were ultimately included for analysis were either randomized trials or non-randomized prospective single-arm studies that described intervention for CLTI patients (Supplemental Table 3). Although most studies focused solely on CLTI, we included studies that included patients with claudication and reported the data pertaining to the subset of patients with CLTI (Supplemental Table 4). We excluded studies that primarily enrolled patients with intermittent claudication (Rutherford class 1-3). We excluded meta-analyses, case series, case reports, abstracts, and expert opinion. Also excluded were studies that examined biological therapies for CLTI (eg, stem cell therapy) (Figure 1).

ENDPOINTS. After identification of the candidate studies, we proceeded to evaluate study methodology. Specifically, we extracted information regarding: 1) primary and secondary endpoints; 2) duration of follow-up; 3) physiological testing; 4) patency assessment; 5) wound assessment; and 6) quality of life (QOL) assessment.

As more than 1 primary endpoint was frequently assessed in a given study, all primary endpoints were recorded (Table 1). Of note, some trials used the

converse of the same outcome (eg, MALE and freedom from MALE). Both rates are reported, but for the purposes of tabular presentation, these were considered under the same categories.

Hemodynamic testing was defined as testing with either ankle-brachial index (ABI) or ABI plus toe brachial index (TBI) and absolute toe pressure measurement.

Anatomical testing was defined as lesion assessment by ultrasonography, invasive angiography, or both modalities.

Wound assessment was stratified as being quantitative, qualitative, or both. Assessment was quantitative if wound measurements were provided. Assessment was defined as qualitative if the study assessed the wound using a wound scoring system such as WIFI (wound, ischemia, and foot infection) (9) and PEDIS (perfusion, extent/size, depth/tissue loss, infection, sensation) (10) or with verbal description.

QOL assessment across the studies was performed using QOL questionnaires. These were collected and tabulated for the purpose of the present review.

RESULTS

The database search yielded 7,216 papers in PubMed and 387 studies in ClinicalTrials.gov. We identified 49 relevant studies (n = 11,667) that fulfilled the inclusion criteria (Figure 1). Of these, 38 studies (8,188 patients) have been published, while 11 studies (3,479 patients) have not been published at the time of collating the data. Among the 49 trials, 29 were randomized controlled trials and 20 were non-randomized. A full list of the studies meeting inclusion criteria is shown in Supplemental Table 2.

PRIMARY AND SECONDARY OUTCOMES. One primary outcome was present in 30 trials (61.2%), while 19 (38.8%) had multiple primary outcomes (Table 1, Supplemental Table 1). There was greater variability in secondary outcome choice and number compared with the primary outcome. In general, there were more secondary outcomes per study. Furthermore, there was much variability in outcome definitions (ie, the same title could pertain to different metrics; Supplemental Table 2).

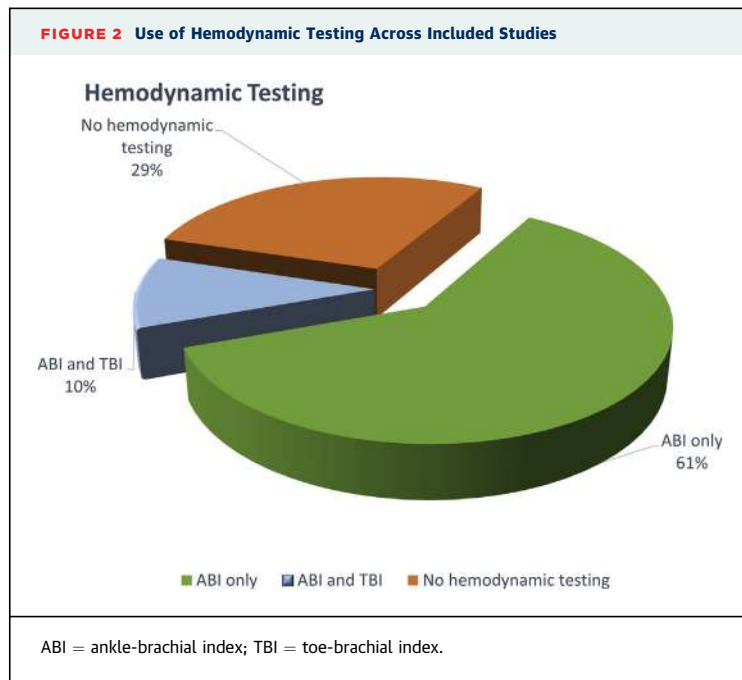
MORTALITY. Mortality was assessed in 69.4% of studies, in 10.2% as a separate primary outcome and in 24.5% as a separate secondary outcome. Mortality was part of a composite outcome in 49.0% of studies. Although the definition of death was constant, composite outcomes that included mortality differed and included AFS, major adverse events, and MALE plus POD.

TABLE 1 Distribution of Outcomes Across All Studies

Primary Outcome	Proportion of All Studies	Comments
Efficacy and safety outcomes		
Death (any assessment)	34/49 (69.4)	
Primary endpoint	5/49 (10.2)	
Part of composite endpoint (either as primary or secondary endpoint)	24/49 (49.0)	18 studies assessed death as composite endpoint only; 6 studies assessed death as either primary or secondary plus composite endpoint
MALE (any assessment)	43/49 (87.8)	
Primary endpoint	12/49 (24.5)	
Part of composite endpoint (either as primary or secondary endpoint)	30/49 (61.2)	11 studies assessed MALE as composite endpoint only; 19 studies assessed MALE as either primary or secondary plus composite endpoint
TLR (any assessment)	41/49 (83.7)	
Primary endpoint	5/49 (10.2)	
Part of composite endpoint (either as primary or secondary endpoint)	22/49 (45.0)	12 studies assessed TLR as composite endpoint only; 10 studies assessed TLR as either primary or secondary plus composite endpoint
Functional and wound endpoints		
Change in Rutherford class	3/49 (6.1)	
Wound healing	3/49 (6.1)	
Unspecified	4/49 (8.2)	No details regarding the metric to assess clinical improvement
Patency		
By angiography	12/49 (24.5)	
By arterial duplex	11/49 (22.5)	
TVAL%	2/49 (4.1)	Currently used by Mercator Medsystems
Procedural and technical success	16/49 (32.7)	
Values are n/N (%). MALE = major adverse limb event(s); TLR = target lesion revascularization; TVAL% = transverse-view vessel area loss percentage.		

MAJOR ADVERSE LIMB EVENTS. Limb events reported as “major adverse limb events” or “MALE” by the trials were assessed in 87.8% of studies, in 24.5% as a separate primary outcome, in 49% as a separate secondary outcome, and as part of a composite outcome in 61.2% of trials. Amputation or AFS was used in 51% of studies. Definitions varied among trials (Supplemental Table 2). Of note, historically AFS was intended to be separate from MALE (7).

HEMODYNAMIC TESTING. Of all studies, 71.4% used hemodynamic testing as part of their methodologies (Figure 2); 10.2% had ABI and TBI assessment, while 61.2% used ABI only. Among the studies in which hemodynamic testing was performed, 34 of 35 studies (97.1%) performed baseline testing. Furthermore, 33 of 35 studies (94.3%) reported testing over several time points; there was significant variability of the follow-up testing intervals ranging from 30 days to 5 years.



PATENCY ASSESSMENT. Forty-four studies (89.8%) had information regarding patency assessment at baseline and/or during follow-up. Patency was part of the primary outcome in 25 of 49 of studies (51%). A total of 65.3% of all studies used duplex ultrasonography (DUS), 85.7% used invasive angiography, and 63.3% used both DUS and invasive angiography. Overall, baseline DUS was performed in 26.5% and baseline angiography was performed in 83.7% of all studies. Of the 44 studies that examined patency, longitudinal follow-up was performed in 40 (90.1%). Methods for longitudinal follow-up included DUS only in 40% (16 of 40), angiography only in 20% (8 of 40), and using both DUS and angiography in 40% (16 of 40).

Figure 3 illustrates the temporal adoption of arterial DUS into the methodology of the included studies for follow-up. DUS was used in 56% of all studies between 2000 and 2009 (binary assessment with DUS flow or no flow performed in 35.7%, assessment of stenosis with peak systolic velocity ratio or other DUS-derived correlating factors in 64.3%) and in 58.3% among the studies performed between 2010 and 2019 (binary assessment with DUS flow or no flow performed in 57.1%, DUS and peak systolic velocity ratio assessment in 42.9%). Interestingly, among the 14 studies published between 2015 and 2019, 11 studies (78.6%) used DUS assessment.

TLR was assessed in 83.7% of trials, in 10.2% as a separate primary outcome, in 57.1% as a separate

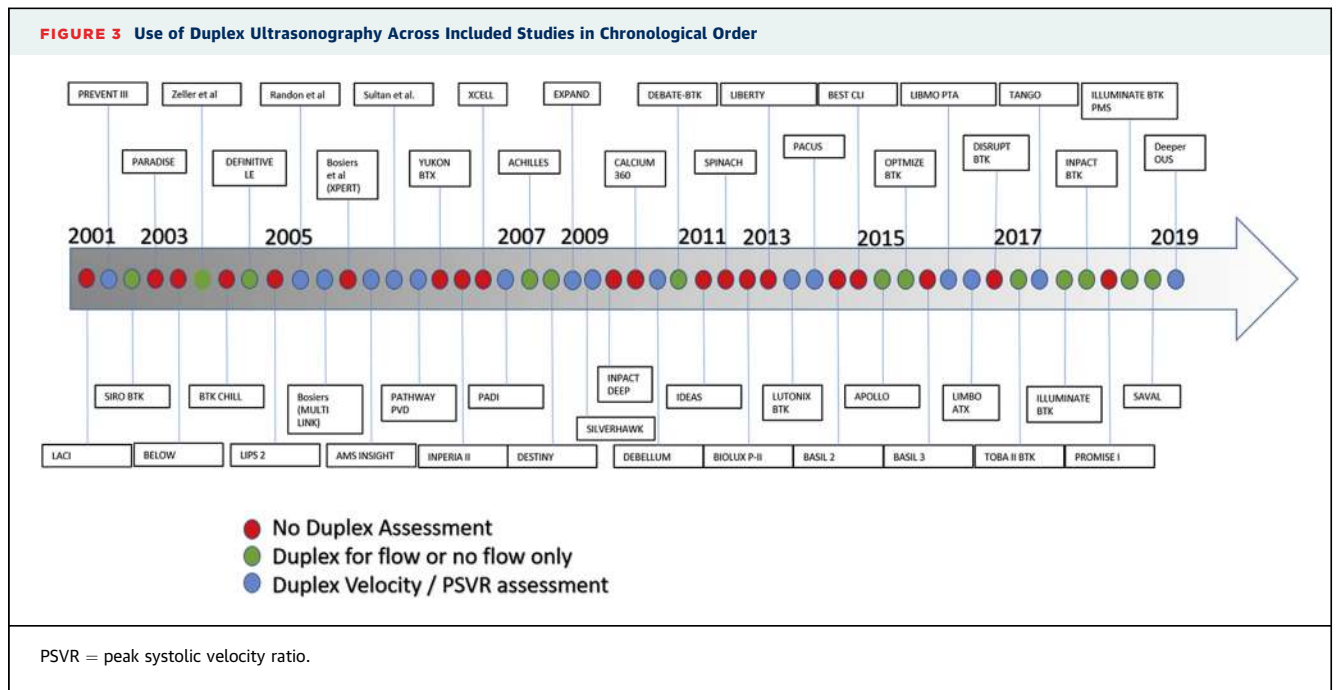
secondary outcome, and as part of a composite outcome in 45%. Importantly, definitions varied and sometimes (eg, clinically driven TLR) were missing altogether ([Supplemental Table 2](#)).

WOUND ASSESSMENT. Wound assessment was performed in 24 of 49 studies (49.0%); evaluation was qualitative in 14 of 49 (28.6%) and quantitative in 10 of 49 (20.4%). Wound healing was part of the primary outcome in 3 of 49 studies (6.1%), and change in Rutherford classification was part of the primary outcome in 3 of 49 studies (6.1%) as well. Among qualitative studies, WifI classification was used most often (20.4% [10 of 49]). Among studies that reported quantitative wound assessment (n = 10), 5 assessed wound surface areas, and 1 study measured the wound manually using a ruler and a photograph; 4 studies did both. Of the 24 studies that performed wound assessment, 21 reported longitudinal follow-up of the wound, which was not necessarily aligned with other endpoints.

QOL ASSESSMENT. QOL assessment was performed in 27 of 49 of all studies (55%); in 13 of the studies (26.5%), more than 1 QOL tool was used. The EQ-5D questionnaires was the most common tool and was used in 17 of 27 trials (63%). A pain scale was reported in 5 of 49 studies (10.2%). When QOL was assessed, longitudinal assessment was present in 24 of 27 studies (89%). Other patient-reported outcomes were not being captured.

DURATION OF FOLLOW-UP. The mean duration of follow-up was 23.7 months (range 1-66 months); 21 of 49 studies (42.9%) reported 12-month follow-up, while 20 of 49 (40.8%) reported longer follow-up durations, and only 8 of 49 (16.3%) reported shorter duration of follow-up. There was significant variation in the duration of follow-up across the studies, with no discernable pattern over time.

In investigational device exemption (IDE) trials, the primary outcome and overall follow-up were often discordant; the median overall follow-up duration was longer than the time to the primary outcome (12 months [IQR: 7.5-12.0 months] vs 6 months [IQR: 1-6 months]; $P = 0.0018$). When comparing pivotal trials with other IDE trials, overall median follow-up time did not differ (12 months [IQR: 9-12 months] vs 12 months [IQR: 6-12 months]; $P = 0.71$). However, the median time to the primary outcome was significantly longer for pivotal compared with other types of trials (6 months [IQR: 6-12 months] vs 1 month [IQR: 0-6 months]; $P = 0.008$).



DISCUSSION

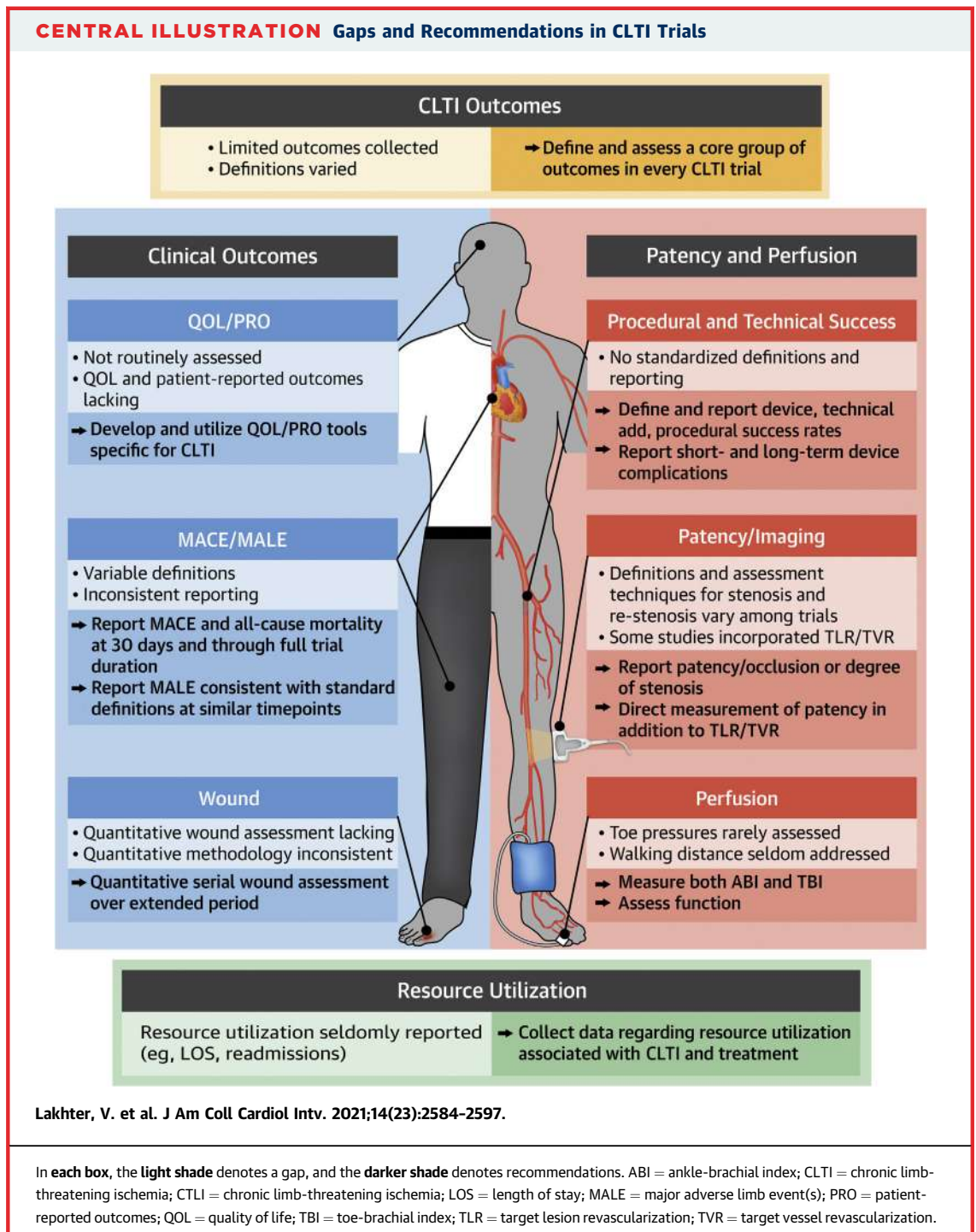
The present analysis offers several important insights into CLTI investigation over the past 2 decades (Central Illustration). Despite variability among studies, especially concerning outcome definitions, there were many common themes. 1) Most trials focused on clinical endpoints: mortality and MALE, including amputation rate and AFS. Of note, historically AFS was not intended to be part of the definition of MALE (7). 2) Mean total follow-up was approximately 2 years (albeit across a wide range of 1-60 months). 3) Hemodynamic testing was used in 71.4% of studies, most often ABI and TBI. 4) Angiography was the most common modality used to report anatomy at baseline. In contrast, longitudinal data, focusing mainly on patency, were available for most studies, using most often DUS. 5) Assessment of wound healing was performed in most studies, but reporting standards were variable. 6) QOL measures were used in about half of the studies. The most common tool was the EQ-5D questionnaire.

OUTCOMES. Most trials captured death, MALE and TLR (Table 1, Supplemental Table 1). Patency was assessed in about half of the trials. However, the definitions of these outcomes varied considerably (Supplemental Table 2). These variations can make comparisons across trials challenging, if not impossible.

Many trials opted for a composite outcome (Table 1). This has merit in the study of CLTI interventions. The relatively high mortality rate of this patient population presents a competing risk to limb-related outcomes (in other words, patients may die before a limb-related outcome, positive or negative, can be detected). Thus, combining mortality with MALE is appealing. Alternatively, a combination of periprocedural complications (including death) and MALE (which includes a measure of reintervention) may be attractive as a representation of periprocedural safety and long-term efficacy (6).

Importantly, functional and wound-related outcomes, although central to patient well-being, were assessed in only 1 in 5 studies. This may be because wound healing is complex and depends on many factors beyond arterial flow.

Next, the primary and secondary outcomes should be mentioned (Table 1, Supplemental Table 1). First, in practice, these outcomes can represent commitments to regulatory bodies. Also, the primary outcome often receives focus in reporting of trial results and when comparing results across trials. The primary outcome should reflect procedural efficacy, patient-related safety, and clinical outcomes. We found that about one third of studies included more than 1 primary outcome. The most common components of the primary outcome were clinical (mortality and MALE) and measures of patency (such as TLR and



patency rate). Still, we found that there was much variability in the composition and definitions of the components primary and secondary outcomes. In this context it should be noted that for many common outcomes standard definitions have been published (7,11,12). Finally, a time point for the primary outcome was often not predefined and did not

always reflect the full time frame during which patients were actually followed (Supplemental Table 1). More recent IDE studies have focused on a 6-month time frame for the primary outcome (13,14). Thus, again, combined with the aforementioned variability in definitions, interpreting results across trials is challenging.

TABLE 2 Core Outcomes Suggested for All CLTI Trials^{a,b,c}

Survival/mortality
All-cause mortality through full trial duration
All-cause mortality through 30 day ^d
Limb-specific events
MALE ^e
Ipsilateral major amputation
Planned and unplanned ipsilateral minor amputation
Adverse clinical events
MACE
Other adverse clinical events (eg, pneumonia, bleeding, postprocedural renal insufficiency)
Minor complication rate ^f
Patency assessment
Primary patency as defined by direct radiologic imaging (eg, duplex ultrasonography, computed tomographic angiography)
Primary assisted patency as defined by direct radiologic imaging
Secondary patency as defined by direct radiologic imaging
Clinically-driven TLR ^g
All TLR
All TVR
Physiologic/hemodynamic parameters
Hemodynamic testing (eg, ankle-brachial index, toe-brachial index)
Quantitative perfusion testing (eg, TcPO ₂)
Wound related
Wound healing rate (ie, total proportion wounds healed, including healing of amputation sites) as documented by serial wound imaging and adjudicated by independent core laboratory examination
Wound healing rate (ie, wound healing over time); documented and adjudicated
Record of all wound debridements/interventions
Wfi scores over time
Quality of life/patient-reported outcomes
Change in Rutherford category (sometimes referred to as “clinical improvement”)
Quality of life instruments ^h
Patient-reported outcomes ^h
Ambulatory status
Independent living status
Pain scale and narcotic use
Resource utilization
Length of hospital stay
Hospital readmissions
Procedure and cumulative costs
QALYs
Procedural and technical success
Device success rate
Technical and procedural success rate (17) ⁱ
Periprocedural complications
Long-term implantable device related adverse events (eg, stent fracture, stent migration, endoleak)

^aBlinded, independent core laboratory adjudication of sonographic or radiologic findings and wound imaging and blinded clinical events committee adjudication of adverse events and certain outcomes such as clinically driven TLR are integral to CLTI trial reporting. ^bSome outcomes that will be reported to regulatory bodies or in publications can be calculated from the outcomes collected (eg, MALE and POD, amputation-free survival, restenosis or occlusion, total number of reinterventions, freedom from adverse events). ^cEvents should include a time stamp (eg, mortality should be reported as intraprocedural, periprocedural, 30 day, long-term). ^dRepresents POD. ^eAbove-the-ankle amputation of the index limb or major reintervention (new bypass graft, jump or interposition graft revision, or thrombectomy or thrombolysis) (7). ^fAs per the Society for Interventional Radiology (44). ^gExamples of clinical indications for TLR include static or worsening wound or pain, declining hemodynamic measurements, or a finding of >70% stenosis of the index intervention. ^hThere are no well-validated CLTI instruments. ⁱProcedural success rate should also document procedure-related complications (eg, distal embolization, dissection, perforation, abrupt vessel closure, access site complications, need for bail-out stenting or surgery).

CLTI = critical limb-threatening ischemia; MACE = major adverse cardiovascular event(s); POD = postoperative death; QALY = quality-adjusted life-year; TcPO₂ = transcutaneous pressure of oxygen; TVR = target vessel revascularization; other abbreviations as in Table 1.

TABLE 3 Gaps and Recommendations	
Gaps	Recommendations
Outcomes Some studies assessed limited outcomes. Definitions for many endpoints (eg, MALE, patency) were variable.	A core group of outcomes should be assessed in every CLTI trial (Table 2). Well-accepted definitions are available for many endpoints and should be adopted (7,17,18).
Hemodynamic and functional testing Toe pressures are rarely assessed. Walking distance is seldom assessed (15,19,45).	We recommend measuring ABI and TBI over multiple time points. We recommend assessment of walking distance with a validated tool (eg, 6-min walk test).
Patency assessment Definitions and assessment techniques for stenosis and restenosis vary across trials. Some studies incorporated TLR/TVR into the definitions of patency.	Trials can choose between two approaches: 1) reporting patency/occlusion of the treated segment; and 2) reporting the degree of stenosis within the treated segment. Direct measurement of patency is recommended, as relying on TLR/TVR may introduce bias.
Wound assessment Wound assessment occurred in 49% of trials wound assessment strategies and reporting varied.	Wound assessment should be reported in patients with Rutherford class 5 and 6 disease. We recommend a comprehensive strategy for serial wound assessment over extended periods of time. Such a strategy must include rigorous and adjudicated quantitative measurements (ie, exact wound surface area) and wound clinical characteristics (eg, granulation tissue and infection).
QOL and PROs QOL was not routinely assessed. PROs are rarely reported. Validated CLTI-specific QOL tools and PROs do not exist.	We recommend collecting data pertaining to QOL in studies assessing the utility of procedures for the treatment of CLTI. We recommend including pain scores and functional outcomes (eg, ambulatory and independent status) (46). QOL tools and PROs specific to CLTI should be developed and validated. Once available, these should be implemented.
Study duration Studies reported outcomes across a wide range (1-60 mo).	Trial duration should allow assessment of mortality, limb-related adverse events, major adverse clinical events, and long-term device efficacy. Although this duration may vary depending on trial-specific characteristics, most trials will require follow-up of several years.
ABI = ankle-brachial index; PRO = patient-reported outcome; QOL = quality of life; TBI = toe-brachial index; other abbreviations as in Tables 1 and 2 .	

Optimally, we would hope for future CLTI trials to expand beyond mortality, MALE, TLR, and patency by collecting a set of “core outcomes” that will include clinical, procedural, and health care utilization data over a long period of time ([11](#)) ([Table 2](#)). Furthermore, although the present review focuses on outcomes, standardizing data collection and reporting of baseline patient characteristics, comorbid conditions and medical therapies as well as enrollment screen failures are also of value. In this context, specific mention is warranted to trials assessing surgical procedures or those comparing surgery with endovascular intervention. A total of 6 trials included surgical arms (Irish trial of critical limb ischemia [[15](#)], PREVENT III [Project of Ex-Vivo Graft Engineering via Transfection III] [[16](#)], BASIL [Bypass Versus Angioplasty in Severe Ischaemia of the Leg] [[17](#)], BASIL 2 [[18](#)], BEST-CLI [Best Endovascular Versus Best Surgical Therapy for Patients With Critical Limb Ischemia] [[19](#)], and SPINACH [Surgical Reconstruction Versus Peripheral Intervention in Patients With

Critical Limb Ischemia] [[20](#)]) ([Supplemental Table 3](#)). The outcome measures used in these studies were not substantially different from those used in other studies in the present analysis ([Supplemental Tables 1 and 2](#)). Indeed, we again advocate for the core outcomes to be collected in such trials. This will allow meaningful comparisons across different trial designs. However, individual trials may need to collect outcomes that reflect the intervention or device being studied (eg, surgical wound healing). Finally, as different interventions may result in different outcome patterns (eg, upfront morbidity associated with surgery vs need for reintervention), patient-reported outcomes, and measures of functional status may have specific great value to allow meaningful comparisons. Also, ideally, exclusion criteria would be minimized. Including different patient populations (eg, presence vs absence of end-stage renal disease) with different lesion characteristics (eg, stenosis vs chronic total occlusion, severe vs minimal calcification) could allow meaningful insight into the

presentation and natural history of CLTI. However, we admit that such studies may not be practical to execute, especially when the goal is to approve a medical device for use (ie, IDE trials). Thus, pragmatically, a study should collect data that are relevant to the procedure (eg, patency, clinically driven TLR, and device-related safety) and to the patient (eg, mortality and AFS). Standardized definitions for the most common outcomes will also be crucial to allow meaningful decisions to be made by clinicians and regulatory bodies (Table 3).

HEMODYNAMIC TESTING AND PATENCY ASSESSMENT.

Perfusion and patency are central measures of intervention in CLTI. Thus, hemodynamic and anatomic testing are important, both pre- and postintervention (21). We found that hemodynamic testing (ABI and TBI) was used often and usually collected longitudinally. Nonetheless, compared with assessment of perfusion in patients with claudication, hemodynamic testing may be limited in CLTI (eg, because of multilevel disease and extensive arterial calcifications), especially in patients who also have diabetes mellitus and renal failure (22,23). Still, hemodynamic studies have the potential to offer clinically useful information, especially if followed over time in a particular patient. In particular, TBI is useful in CLTI and can serve as a surrogate for overall hemodynamic efficacy.

DEFINING PATENCY. Although patency is central to clinical outcomes in CLTI (24), measuring patency in CLTI can be challenging. In theory, repeat angiograms could offer this information. Indeed, about half of the studies used angiography postprocedurally, usually at 1 time point. When angiography was available, the most common measure was stenosis severity > 50% or <50%. Still, widespread implementation of angiography over multiple time points is impractical for obvious safety concerns. Also, computed tomographic angiography and magnetic resonance angiography are of limited use because of renal function impairment, calcifications, and limitations concerning spatial resolution. Thus, in practice, DUS was used in 80% of studies to measure patency over time, typically at multiple time points.

With DUS, some studies collected only information on any flow to the ankle, while others assessed target lesion patency (Figure 3). Also, definitions of DUS-derived target lesion patency were variable. They ranged from using a calculated peak systolic velocity ratio between the lesion and a normal segment upstream from it to a more robust assessment that also included correlating factors such as B-mode, color

flow imaging, and spectral waveform analysis proximal, within the lesion and distal to it. Indeed, these techniques are very well validated in the femoral and popliteal arteries (25,26) and in patients who have undergone surgical bypass grafting (27) and are commonly extrapolated to define patency in below-the-knee arteries (28-30).

Finally, it should be noted that substituting patency for TLR (or target vessel revascularization) might introduce bias, because in many trial designs, investigators are not blinded to the interventions patients undergo. Thus, we advocate continuing to measure patency directly. Although we recommend implementing these principles, more validation of these methods is required. Importantly, in the absence of thoroughly validated DUS assessment of below-the-knee arterial stenosis, many IDE trials have favored using a “patent versus occluded” (essentially binary) assessment of antegrade flow throughout the treated lesion.

WOUND ASSESSMENT. Most CLTI trials enroll patients with rest pain or nonhealing ulcers. However, the ability to durably restore patency and increase perfusion does not guarantee wound healing. In fact, the extent to which hemodynamic changes, post-intervention patency, and the durability of revascularization affect wound healing is poorly understood. In practice, achieving wound healing requires a multifaceted approach, which is variable across trials and sites and is difficult to standardize (31,32). Nonetheless, wound healing is an important outcome for patients with CLTI. Still, despite available regulatory body guidance (33), there is no consensus as to how wound healing should be assessed, and as such, protocols differ considerably.

The Rutherford classification (34) was used in most studies. This scoring system neither quantifies tissue loss nor describes wound characteristics. Wound-specific clinical scoring systems were used in fewer than half of the studies (eg, WIfI was used in 10 of 49, though it should be noted it was only published in 2014 [9], and most studies published after this time did use this classification). Furthermore, only a minority of studies assessed wounds quantitatively over time. In this context, one must remember that although arterial patency is related to wound healing, the relationship is indirect. Complete wound healing is affected by many factors, including wound size, complexity, and associated complications (eg, infection). Thus, CLTI trials, including IDE trials, should follow objective wound-related metrics. Wound healing rate should deserve specific mention. Clinically, faster wound healing allows more rapid

rehabilitation and return to functional activity (35). As wounds differ in size and complexity, wound healing rate can allow comparisons across wounds and trials. Nevertheless, many of the trials we evaluated implemented only a simple wound progress assessment that categorizes a wound as completely healed, improved, unchanged, or worsening or indicates that the limb was amputated.

It follows that a quantitative assessment of wound healing should include longitudinal wound surface area and report of clinical measures, such as granulation tissue and presence of infection (35,36). Efforts should be made to standardize the reporting of these endpoints, to minimize subjectivity in interpretation of findings. Also, especially as wound healing is affected by more than revascularization alone, incorporating functional outcomes (eg, measures of ambulation) may also be useful to characterize the effect a wound (residual or healed) has on patient-centered outcomes. Finally, as microvascular disease has been linked to amputation in PAD (37), there is much appeal to measuring periwound perfusion. Although multiple technologies have surfaced, none have yet to become ubiquitous, and a common scheme for characterization of perfusion has yet to emerge. These technologies have not been used in any of the studies that we evaluated.

QUALITY OF LIFE. Patient-reported outcome measures are being promoted for use both in research and in clinical practice. Unfortunately, validated measures are currently lacking (38). Also, shared decision making as part of the consent process should be mentioned in the context of patient-centric outcomes. These are yet to gain traction in the study of CLTI. Still, measures of QOL, many of which relevant to patients' overall sense of well-being, were available in about half of the studies. Measures of pain (eg, analog pain scale) were reported in 5 of 49 studies (10.2%). VascuQol is a tool specific for vascular disease and is most commonly used to report patient-reported outcomes for patients with CLTI. However, some have suggested that VascuQol has been inadequately validated for use in PAD (39) and, more recently, in CLTI (40). In fact, in the studies we evaluated, the EQ-5D tool was used most frequently. Still, although it has been validated in PAD, it has not been specifically validated for CLTI (41,42). This tool also provides utility values, an important component of health economic analyses (43).

STUDY DURATION. The current review focuses on outcomes used in critical limb ischemia trials. However, study duration is not an outcome but rather an

element of trial design. Still, the frequency of data collection and overall study duration are likely influenced by the nature of the type of intervention being studied, trial design (eg, industry sponsored or investigator initiated), the preferences of those designing the trials, and the financial commitments of the sponsor. Sponsors of interventional device trials might favor a shorter trial to limit expense and complexity. However, there are advantages to longer studies, including robust assessment of device durability. In practice, study duration is variable and is likely a result of discussion with regulatory bodies during the study planning phase. In some cases, the pivotal cohort will be followed for longer durations. For instance, the primary outcome of pivotal trials was longer than for nonpivotal IDE trials. Other times, different patient populations will be included and followed in postmarket studies.

Many patients with CLTI are elderly and have multiple medical comorbid conditions. Thus, as noted earlier, life expectancy may be impaired on this basis, irrespective of their limb-threatening disease. As such, often the primary outcome is appropriately selected at a relatively short time frame, such as 6 months. Still, although device approval may hinge on success to meet short-term primary outcomes, clinical decision making may need to consider other potential long-term consequence of using one technology or another.

IDE TRIALS VERSUS OTHER TYPES OF TRIALS. Of the 49 trials included in the present review, 23 were IDE trials and 26 were not (Supplemental Table 5). Various trial designs (ie, observational, randomized, etc) were implemented in both IDE and in non-IDE trials (Supplemental Table 3). Specifically, there were 13 randomized IDE trials, of which 9 were pivotal and 4 were feasibility or pilot trials. Although the endpoints in IDE trials must reflect device effectiveness and safety, and should consider patient-related outcomes, they are also designed to be achievable and measurable across sites. Typical primary endpoints include a measure of patency (and/or TLR) together with a measure of MALE, often at a relatively short time frame (ie, 6-12 months). Also, these studies typically opt for strict inclusion and exclusion criteria to reduce unanticipated variability. It follows that patients with rest pain and simpler wounds are usually included, whereas patients with extensive gangrene, complex wounds, and comorbid conditions such as end-stage renal disease are often excluded. Thus, in practice, patency often receives greater prominence when results are reported, while wound and limb salvage-related outcomes are often limited in IDE trials. Furthermore, improved primary

patency may not generate a detectable signal in limb outcomes in a carefully followed IDE cohort when secondary interventions are undertaken promptly and patency rates from secondary interventions are high. Taken together, these factors may limit our understanding of the treatment and its clinical impact beyond achieving marketing approval.

Nonetheless, overall (primary and secondary) endpoint selection was similar between IDE and non-IDE trials (Supplemental Table 1). Still, there were a few important differences. First, more non-IDE trials focused on clinical outcomes such as sustained clinical improvement, wound healing, and QOL. Second, the duration of follow-up, especially for the primary outcome, was substantially longer for non-IDE trials. Finally, most IDE trials adjudicated outcomes using independent core laboratories, while most non-IDE trials did not (Supplemental Table 5). As non-IDE trials are not directly tied to regulatory requirements, they can include a broader patient population and focus more on patient-centric outcomes, over a longer period compared with IDE trials. Objective core laboratory adjudication of angiography, ultrasonography, hemodynamic studies, and wound progression can serve to validate results and standardize reporting across studies.

Separately, although each study design is tied to specific objectives, it is also true that some IDE trials collect data that do not result in regulatory submission for device approval (or publication). For instance, a sponsor of an IDE trial following patients long term under a mandate to collect survival and safety data may also collect other data contemporaneously. In theory, these data can be made available to researchers to add to real-world evidence pertaining to CLTI.

RECOMMENDATIONS. A summary of gaps and recommendations can be found in Table 3. Furthermore, with the hope of promoting standardization and collaboration in the field, we advocate early and open discussion with regulatory bodies while planning a study strategy.

The main strength of this analysis is the duration of inclusion of trials, the level of detail reported, and the limitations to the existing body of research.

However, there are also limitations that need to be outlined. Mainly, although often we did have access to the full trial protocols, sometimes we did not. This may have resulted in some incomplete reporting. Similarly, we were not privy to internal discussions that led to the use of one study method versus another or to discussions between individual manufacturers and regulatory bodies. As many trials are being performed for the purpose of device approval, understanding the role of regulatory requirements is important. Importantly, the US Food and Drug Administration, Centers for Medicare and Medicaid Services, and other payers have repeatedly demonstrated interest in improving the outcomes of patients with CLTI.

CONCLUSIONS

The field of CLTI is a field in evolution. Consensus regarding the ideal outcomes to be studied, their definitions, and optimal methods to measure some of these outcomes are yet to be established. Although ambitious, a robust, coordinated, and comprehensive effort by all stakeholders is needed to move the field of CLTI and related therapies forward in a truly meaningful fashion.

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Dr M.D. Weinberg is a consultant for Boston Scientific, Cardiovascular Systems Inc., Medtronic, Magneto, and Neptune Medical. Dr Geraghty is a consultant for Boston Scientific, Bard, and Ascension Health Ventures; and holds equity in Euphrates Vascular and MedAlliance. Dr Jaff is a consultant for Glide Healthcare; is a part-time employee of Boston Scientific; and is an equity shareholder in R3 Vascular, Embolitech, and Efemoral. Dr Schneider is a consultant for Silk Road Medical, Surmodics, Medtronic, Philips, Boston Scientific, Cordis, Cardiovascular Systems Inc., Cagent, and Philips. Dr I. Weinberg is a consultant for Magneto; and national principal investigator for the STRIKE-PE trial (Penumbra). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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APPENDIX For supplemental tables, please see the online version of this paper.