A Systematic Review of Clinical Trials in Patients With Critical Limb-Threatening Ischemia

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On behalf of the Critical Limb Ischemia Global Society Publications Committee

Abstract

Peripheral arterial disease is a growing global burden, with chronic limb-threatening ischemia (CLTI), its most advanced stage, associated with high morbidity, mortality, and economic costs. While randomized controlled trials are the gold standard for evaluating treatment strategies, their external validity is often limited by strict inclusion criteria that exclude complex, real-world patients with CLTI. Lesion and device characteristics further complicate trial generalizability, with registries providing more representative insights. Recent trials highlight the challenges of translating trial findings to clinical practice. This review underscores the need for evidence-based pathways tailored to real-world CLTI populations.

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Key words: peripheral arterial disease, chronic limb-threatening ischemia, clinical trials

Peripheral arterial disease (PAD) is a chronic and multifaceted disease process that continues to increase in prevalence globally. The estimated number of PAD patients worldwide increased by nearly 25% from 2000 to 2010, with a global burden of 202 million cases in 2010 that is likely underestimated.[1] Chronic limb-threatening ischemia (CLTI) represents advanced, end-stage PAD and is associated with high morbidity and mortality rates. A recent analysis found that within the first year of diagnosis, approximately 29% of patients with CLTI will either die or undergo major amputation, and only an estimated 46% of patients with CLTI will survive over a 4-year period.[2] Due to the complexity of the CLTI disease process and grave clinical prognosis, patients with CLTI frequently have a poor quality of life, and the economic burden of lifelong disease management is significant.[3]

While consensus exists that revascularization for CLTI is necessary to preserve limb function and prolong survival,[4] there is considerable variation in the determination of best treatment practices. The continued refinement of evidence-based treatment pathways is essential in optimizing consistent care for patients with CLTI worldwide. This review focuses on some of the major differences between patients in randomized controlled trials (RCTs) and real-world patients with CLTI.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[5]

Information Search and Selection Process

A search of the literature was done from PubMed and MEDLINE databases and the Cochrane Library through September 2024. Query terms were "(CLI OR CLTI OR PAD) AND (RCT OR 'Randomized Controlled Trial')". The papers identified through the search were uploaded to Covidence, an online platform designed to facilitate systematic reviews.[6] Two independent reviewers screened the title and abstract of each paper, selecting those that either met the inclusion criteria or required further assessment. Following this initial screening, a full-text review was conducted on the selected papers. Any disagreements between reviewers were resolved through discussion to reach a consensus.

Eligibility Criteria

To be eligible for inclusion, studies had to report on RCTs involving patients with CLTI and focus on intervention options for this population. We excluded prospective or retrospective observational studies, systematic reviews, studies not involving

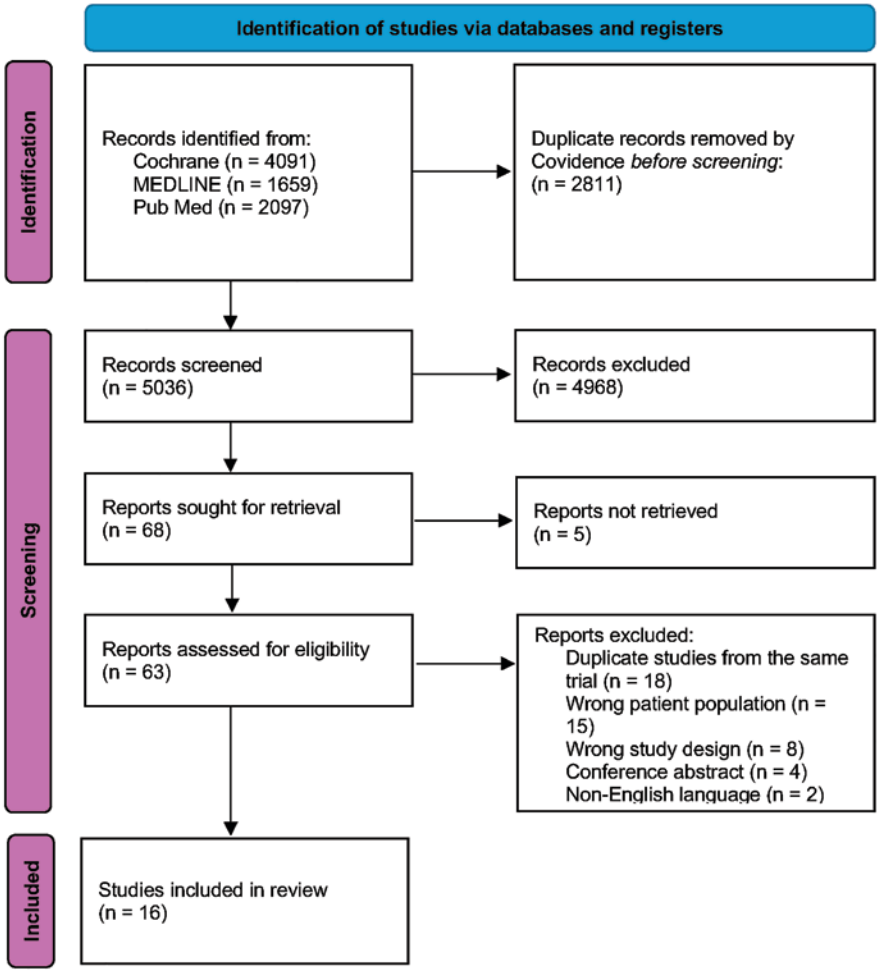

FIGURE. PRISMA flow diagram for assessment of eligible studies.

patients with CLTI, and those focusing on nonperipheral vascular interventions. Manuscripts written in languages other than English and conference proceedings were also excluded. Additionally, when multiple manuscripts reported on the same trial, only the primary trial manuscript was included.

Data Collection and Extraction

From each eligible article, data were collected on the following: article title, first author, trial name, categories of randomized cohorts, primary endpoint, sample size, mean patient age (in years), sex, and key demographic factors such as hypertension, hyperlipidemia, chronic kidney disease (CKD), end-stage renal disease (ESRD), diabetes, stroke, coronary artery disease (CAD), and smoking status. When reported, mean percent stenosis and mean lesion length were recorded.

Results

The initial search of the PubMed and MEDLINE databases and the Cochrane Library yielded a total of 7847 articles (**Figure**). After removing duplicates and conducting an initial screening to exclude unrelated studies, 68 articles were included for further evaluation. Of these, 18 were excluded for being secondary publications from the same trial, 15 for focusing on non-CLTI patients, 8 for being observational studies, 5 because they could not be retrieved, 4 for being conference proceedings, and 2 for being written in languages other than English. This left 16 articles that were included in the final analysis.[7–22]

Study Characteristics

Among the included studies, 9 RCTs compared percutaneous transluminal angioplasty (PTA) to stents for lower extremity revascularization, 3 compared surgical bypass to endovascular techniques, 3 examined drug-coated balloons (DCB) vs PTA, and 1 study compared DCB with laser debulking (LD) to DCB without LD.

Although these studies targeted similar patient populations, their primary endpoints varied. Five studies investigated primary patency; 2 assessed amputation-free survival; 2 focused on restenosis rate; 2 examined a composite of death, amputation, and revascularization; 1 evaluated a composite of major adverse limb events; 1 assessed amputation rate; 1 analyzed late lumen loss; 1 measured improvement in Rutherford category; and 1 assessed the absence of clinical complications. All studies included patient demographic data, with 11 studies reporting percent stenosis at presentation and 13 studies assessing lesion length.

Patient Characteristics

The dataset included 4247 patients (**Table 1**). Among them, 3070 (72.3%) were men, 3237 (80.5%) had a history of hypertension, and 2792 (65.7%) had a history of diabetes. CKD was reported in 9 studies, with 498 patients (16.0%) identified as having the condition. ESRD was reported in 4 studies, involving 136 patients (25.0%) with a history of ESRD. Regarding lesion location, 3 studies included infrainguinal lesions, which involved the superficial femoral artery (SFA), popliteal artery, and below-the-knee lesions. Two studies assessed SFA lesions, and 11 studies examined infrapopliteal lesions only.

Discussion

Methodological Considerations Around RCTs

RCTs have been the foundation of evaluating treatment strategies. They serve as the most robust approach in determining whether a cause-and-effect relationship truly exists between a given treatment and its associated outcome. Typically, RCTs consist of multiple arms that involve comparison between certain treatments, regardless of whether or not the patients received the allotted treatment (intention-to-treat analysis). The analysis is focused on assessing the magnitude of the difference in predefined outcomes between intervention groups.[23] When designing and conducting a RCT, some considerations must be taken into account to ensure that the final result will be methodologically robust (ie, valid) and clinically relevant (ie, generalizable). Generally speaking, while internal validity of RCTs is high (provided they are well-designed and well-executed), external validity and general applicability of RCTs remain problematic.

The issue of trial population not representing real-world patients has been a concern for a significant number of clinicians, as randomized patients in trials tend to have a controlled set of variables. Experiments are designed and conducted to answer specific questions and avoid any unforeseen bias. Consequently, this has brought about concern regarding the applicability of these trial findings to the overall patient population.

Lesion Characteristics in Registries and Retrospective Analyses

The complicated anatomical nature of disease distribution within the peripheral vessels makes comparison between trials nearly impossible; therefore, registries are more representative of real-world patients. Regarding lesion length, in the Peripheral RegIstry of Endovascular OutcoMEs (PRIME) registry, the overall average lesion length was 16 cm with an average of 1.5 lesions treated per intervention.[24] Similarly, the mean lesion length was 12 cm in the IN.PACT Global registry[25] and approximately 9 cm in the BIOLUX P-III registry (**Table 2**).[26] In the Tibiopedal Artery Minimally Invasive (TAMI) retrograde revascularization trial, complex lesions ranged in length between 200 mm and 300 mm.[27] However, in other analysis, such as the Chronic Total Occlusion Approach Based on Plaque Cap Morphology (CTOP) trial, the average chronic total occlusion (CTO) length ranged from 240 mm to 260 mm.[28] In another recent real-world CTO registry of 1516 consecutive patients from Germany, mean lesion length was shown to be 240 mm, similar to the real-world trials mentioned above.[29] It is important to note that an analysis was performed on different types of CTOs that were enrolled within the PRIME registry, where the authors confirmed an average lesion length of 200 mm. Morbidity is noted to worsen with longer lesions, as more distal disease suggests involvement of the tibial arteries and extension of the CTO across multiple vascular beds.[30]

Device Characteristics

Most trials that have evaluated DCB or drug-eluting stents have mainly enrolled patients with claudication rather than CLTI (as a matter of fact, only subgroup analyses of patients with CLTI from these trials are available thus far), thereby calling into question whether potentially limb-saving drug-eluting technology should be avoided in the setting of CLTI. Most RCTs were initially designed to determine technical endpoints, such as target lesion revascularization or primary patency, rather than mortality. Contemporary trials comparing surgical and endovascular approaches in the treatment of patients with CLTI demonstrate conflicting results. In the Surgery or Endovascular Therapy for Chronic Limb-Threatening Ischemia (BEST-CLI) study, it was shown that venous bypass appears to be superior to endovascular therapy in patients with femoral-popliteal lesions who were ineligible for surgical treatment due to multilevel CTOs. However, this was not the case for synthetic conduit bypass.[22] Yet, in the vein bypass first vs a best endovascular treatment first revascularization strategy for patients with CLTI who required an infrapopliteal bypass, with or without an additional more proximal infrainguinal revascularization procedure to restore limb perfusion (BASIL-2) trial, it was shown that an endovascular approach demonstrated a significant reduction in mortality compared to a surgical approach.[10] The difference observed in the primary combined endpoint was primarily driven by the reduction in mortality. Unlike the BEST-CLI trial, BASIL-2 did not require patients to have an adequate autologous vein conduit or to be good surgical candidates, which may have influenced the applicability of its findings. In addition, these trials do not report real-world concerns such as patient quality of life and wound healing, which are often the goal of treating CLTI.

Outcomes

The recent COMPASS and VOYAGER trials have introduced a new powerful combination to reduce intervention and cardiovascular related risk(s) in PAD patients, but their external validity has been questionable.[31,32] In the French COPART registry, it was observed that, among hospitalized patients with symptomatic lower extremity arterial disease, the low-dose rivaroxaban plus aspirin combination used in these trials could not be implemented in many cases due to various practical limitations.[33] As a result, those who were eligible may potentially experience greater absolute benefit because these patients are deemed higher risk than those enrolled in the trials. This leads to questions regarding outcomes of revascularization in patients with CTLI in the hospital vs outpatient setting,[34] with a provider base demonstrating variable experience. These RCTs did not include a control arm that is consistent with contemporary best medical practices and therapy, were funded by industry, and measured a primary outcome that was a composite not based upon the views or experiences of the patients. In addition, in most RCTs patients are only enrolled after successful lesion crossing. As a result, the true failure rate of endovascular attempts is often

Table 1. Summary of study characteristicss

First author	Trial	Group 1	Group 2	Primary endpoint	Patients (n)	CLTI (%)	Group 1	Group 2	Age – years (mean ± SD)	Males n (%)
Adam 2005	BASIL	Balloon angioplasty	Bypass surgery	Amputation-free survival	452	100	224	141	75 years* [IQR 67-82]	272 (60)
Ahn 2023	-	Self-expanding stent	POBA	Amputation rate at 1 year	119	100	58	61	67.6 ± 9.3	100 (84)
Bosiers 2009	AMS INSIGHT	PTA	AMS	Absence of clinical complications at 1 month post procedure	117	100	57	60	73.9 ± 8.2	72 (62)
Bradbury 2023	BASIL-2	Vein bypass group	Endovascular	Amputation-free survival	345	100	172	173	72.5 years* [IQR 62.7-79.3]	280 (81)
Spreen 2016	PADI	PTA ± BMS	DES	Primary binary patency per treated lesion at 6 months	137	100	64	73	73.6 ± 12.0	96 (70)
Chalmers 2012	SMART	Nitinol stent	PTA	Restenosis rate at 1 year	150	18	74	76	67.9 ± 8.9	123 (82)
Fanelli 2012	DEBEL-LUM	DEB	AB	Late lumen loss at 6 months	50	100	25	25	67.0 ± 21.0	37 (74)
Gandini 2013	-	LD + DEB	DEB	Patency at 12 months	48	100	24	24	72.7 ± 7.8	39 (81)
Siablis 2014	IDEAS	DES	PCB	Target lesion restenosis >50% at 6 months	50	NR	25	25	71.5 ± 9.7	38 (76)
Patel 2021	SINGA-PACLI	DCB	PTA	Primary patency of target lesion at 6 months	138	100	70	68	62.5 ± 10.0	79 (67)
Rand 2011	InPeria II	PTA	Stent	Patency rate 6 months after procedure	88	100	44	44	71.8±8.7	88 (66)
Schulte 2015	EXPAND	Stent	PTA	Rutherford category improvement at 12 months	92	64	45	47	72.9 ± 9.5	62 (67)
Overhagen 2023	SAVAL	DES	PTA	Primary patency at 12 months	201	100	130	71	73.0 ± 9.8	150 (75)
Zeller 2020	IN.PACT DEEP	DCB	PTA	Composite of all-cause death, major amputation, and CD-TLR rate assessed through 60 months	358	100	239	119	72.8 ± 8.8	266 (74)
Zeller 2015	BIOLUX P-II	DEB	PTA	Composite of all-cause death, major amputation, and CD-TLR rate assessed 30 days	72	79	36	36	71.3 ± 9.6	57 (79)
Farber 2022	BEST-CLI	Group 1: Surgery Group 2: Surgery	Group 1: Endovascular therapy Group 2: Endovascular therapy	Composite of a major adverse limb event	Group 1: 1434 Group 2: 396	100	Group 1: 718 Group 2: 197	Group 1: 716 Group 2: 199	Group 1: 66.9± 9.9 Group 2: 68.6 ± 9.2	Group 1: 1026 (72) Group 2: 285 (72)

*Median [IQR]

Abbreviations: CLTI, chronic limb-threatening ischemia; HTN, hypertension; HLD, hyperlipidemia; CKD, chronic kidney disease; ESRD, end-stage renal disease; CAD, coronary artery disease; SD, standard deviation; IQR, interquartile range; POBA, percutaneous old ballon angioplasty; PTA, percutaneous transluminal angioplasty; AMS, absorbable metal stent; BMS, bare metal stent; DES, drug-eluting stent; SFA, superficial femoral artery; DEB, drug-eluting balloon; AB, angioplasty balloon; LD, laser debulking; DCB, drug-coated balloon; PCB, paclitaxel-coated balloon; CD-TLR, clinically driven target lesion revascularization.

Table 1. Summary of study characteristicss

HTN n (%)	HLD n (%)	CKD n (%)	ESRD n (%)	Diabetes n (%)	Stroke n (%)	CAD n (%)	Smoking n (%)	Stenosis-% (mean ± SD)	Lesion Location	Lesion length - mm (mean ± SD)
275 (61)	152 (34)	-	-	190 (42)	97 (21)	79 (17)	164 (36)	-	Infrainguinal	-
77 (65)	7 (6)	31 (26)	21 (18)	98 (82)	17 (14)	31 (26)	29 (24)	>50%	Infrapopliteal	POBA: 83 ± 71.8 Stenting: 69.4 ± 61.4
102 (87)	67 (57)	-	-	82 (70)	-	-	50 (43)	PTA: 69 ± 12% AMS: 69 ± 11%	Infrapopliteal	PTA: 12.0 ± 5.0 AMS: 10.6 ± 4.9
257 (76)	267 (79)	118 (34)	-	237 (69)	59 (17)	64 (19)	71 (21)	-	Infrapopliteal	-
-	-	-	37 (27)	87 (64)	25 (18)	52 (38)	33 (24)	PTA±BMS: 83.1 ± 16.7 DES: 83.2 ± 15.3	Infrapopliteal	PTA ± BMS: 23.1 ± 21.8 DES: 21.1 ± 19.3
100 (67)	-	-	17 (11)	52 (35)	-	58 (39)	38 (25)	>70%/ occluded	SFA	Stent: 123.0 ± 54.3 PTA: 116.8 ± 52.2 F
34 (68)	29 (58)	-	-	22 (44)	-	-	31 (62)	85.0 ± 6.4	Infrainguinal	75 ± 35
39 (81)	39 (81)	9 (19)	-	48 (100)	9 (19)	15 (31)	32 (67)	-	SFA	LD + DEB: 22.4 ± 9.4 DEB: 25.9 ± 8.7
25 (50)	23 (46)	19 (38)	-	35 (70)	-	14 (28)	15 (30)	86.1 ± 9.4	Infrapopliteal	137.5 ± 51.3
97 (83)	99 (85)	-	61 (53)	110 (94)	26 (19)	69 (59)	41 (36)	80.0 ± 17.8	Infrapopliteal	86.1 ± 72.6
-	-	-	-	69 (78)	-	-	-	69.5 ± 21.0	Infrapopliteal	20.9 ± 16.8
87 (94)	63 (69)	38 (41)	-	63 (69)	33 (36)	41 (45)	43 (47)	76.2 ± 17.7	Infrapopliteal	36.9 ± 31.7
174 (87)	153 (76)	33 (16)	-	127 (63)	-	-	45 (22)	77.9 ± 17.2	Infrapopliteal	68.3 ± 40.5
320 (89)	255 (71)	34 (9)	-	263 (74)	122 (34)	70 (20)	183 (51)	-	Infrapopliteal	111.0 ± 92.1
62 (86)	49 (68)	20 (28)	-	48 (67)	22 (31)	30 (42)	40 (56)	72.3 ± 24.2	Infrapopliteal	114.1 ± 87.1
Group 1: 1238 (87) Group 2: 350 (89)	Group 1: 1041 (73) Group 2: 299 (76)	Group 1: 151 (11) Group 2: 45 (11)	-	Group 1: 1023 (72) Group 2: 238 (60)	Group 1: 190 (13) Group 2: 62 (16)	Group 1: 617 (43) Group 2: 204 (52)	Group 1: 509 (36) Group 2: 140 (35)	-	Infrainguinal	-

*Median [IQR]

Abbreviations: CLTI, chronic limb-threatening ischemia; HTN, hypertension; HLD, hyperlipidemia; CKD, chronic kidney disease; ESRD, end-stage renal disease; CAD, coronary artery disease; SD, standard deviation; IQR, interquartile range; POBA, percutaneous old ballon angioplasty; PTA, percutaneous transluminal angioplasty; AMS, absorbable metal stent; BMS, bare metal stent; DES, drug-eluting stent; SFA, superficial femoral artery; DEB, drug-eluting balloon; AB, angioplasty balloon; LD, laser debulking; DCB, drug-coated balloon; PCB, paclitaxel-coated balloon; CD-TLR, clinically driven target lesion revascularization..

Table 2. Summary of patient and lesion characteristics across major peripheral artery disease registries

Registry	Design	Device	Patients (n)	Age - years (mean ± SD)	Males n (%)	CLTI (%)	Stenosis (%)	Mean lesion length (mm)	Lesion location
PRIME	Multicenter, prospective, observational	NR	328	70.3 ± 11.7	211 (64.3)	100	92.7 ± 10.7	156.1 ± 130.9	Above the knee (22%), below the knee (35%), multilevel (23.2%)
IN.PACT Global	Multicenter, prospective, observational	IN.PACT Admiral DCB (Medtronic)	1406	68.6 ± 10.1	953 (67.8)	11	88.8 ± 12.3	121.0 ± 95.0	Femoro-popliteal
BIOLUX P-III	Multicenter, prospective, observational	Passeo-18 lx DCB (Biotronik)	877	70.1 ± 10.2	561 (64.0)	42	86.9 ± 12.9	89.0 ± 77.0	Femoro-popliteal (75.4%), infra-popliteal (17.0%)

Abbreviations: CLTI, critical limb-threatening ischemia; NR, not reported; DCB, drug-coated balloon.

underreported. Similarly, observational registries typically enroll patients only after successful treatment, further contributing to selection bias and limiting generalizability.

Patients With Critical Limb-Threatening Ischemia in RCTs vs Real-World Patient Populations

RCTs carry the burden of tackling very complex disease processes such as PAD but often exclude the most complex patients and lesions. For example, although the BEST-CLI study demonstrated that venous bypasses and conduits are superior to endovascular therapies, it is important to consider that it is not uncommon for patients to have undergone previous coronary artery bypass grafting where saphenous vein was already harvested.[35]

Patients with CLTI carry high levels of morbidity and mortality. The complex nature of these patients extends from their clinical history, which includes CAD, cerebrovascular disease, diabetes, heart failure, and CKD, especially those with ESRD on hemodialysis, that will certainly limit patient inclusion in research trials. Several groups have utilized fewer selected data from large administrative registries to confirm or confute controversial claims. It has become increasingly important to analyze inherent selection bias in trials that may become clinically relevant. For instance, it is well-known that RCTs tend to enroll fewer women when compared with observational registries.[20] This highlights the ongoing need to address selection bias and improve the generalizability of trial findings to better reflect real-world patient populations.

Conclusion

This review shows that while RCTs remain essential for generating high-quality evidence and guiding therapeutic decisions, their results do not always fully capture the complexity of real-life clinical scenarios. This gap is particularly evident in the care of patients with CLTI, where translating RCT findings to everyday practice can be challenging. Caution should be taken when applying the results to real-world patient populations. It remains a major concern when clinicians are expecting similar outcomes to RCTs when treating real-world patients with CLTI. A more realistic RCT should include real-world patients with CLTI and address these important and challenging questions by incorporating diverse patient cohorts. Future research should include all patient populations that are under-represented in current literature.

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