The natural history of untreated severe or critical limb ischemia

Abd Moain Abu Dabrh, MBBCh, MS,[a,b] Mark W. Steffen, MD, MPH,[a] Chaitanya Undavalli, MBBS,[b] Noor Asi, MD,[b] Zhen Wang, PhD,[b] Mohamed B. Elamin, MD,[b] Michael S. Conte, MD,[c] and Mohammad Hassan Murad, MD, MPH,[a,b] *Rochester, Minn; and San Francisco, Calif*

Objective: **Critical limb ischemia (CLI) is associated with high morbidity and mortality. Because most patients with CLI will eventually undergo some type of revascularization, the natural history of CLI is not well defined, although it is important to know when patients decide to pursue treatment.**

Methods: **We systematically searched multiple databases for controlled and uncontrolled studies of patients with CLI who did not receive revascularization with a minimum follow-up of ≥1 year. Predefined outcomes of interest were mortality, major amputation, and wound healing. Random-effects meta-analysis was used to pool cumulative incidence across studies.**

Results: **We identified 13 studies enrolling 1527 patients. During a median follow-up of 12 months, all-cause mortality rate was 22% (confidence interval [CI], 12%-33%) and major amputation rate was 22% (CI, 2%-42%). Worsened wound or ulcer was found at 35% (CI, 10%-62%). There was a trend toward improvement in mortality and amputation rate in studies done after 1997. The quality of evidence was low because of increased risk of bias and inconsistency.**

Conclusions: **Mortality and major amputations are common in patients who have untreated CLI during a median follow-up of 1 year, although these outcomes have improved in recent times. (J Vasc Surg 2015;62:1642-51.)**

Peripheral artery disease is a chronic condition that causes compromised blood flow to the extremities. It is estimated that 5% to 10% of patients with peripheral artery disease older than 50 years develop critical limb ischemia (CLI) within 5 years.[1] The European consensus document defines CLI as persistently recurring ischemic rest pain or ulceration, or gangrene of foot or toes, lasting >2 weeks.[2] Recent reports estimated that the annual incidence of CLI in Europe and the United States ranges between 500 and 1000 new cases per million persons.[3]

Morbidity and mortality associated with CLI are high. Whereas there are several approaches to management of CLI, including risk modification techniques, exercise, and pain and ulcer management, revascularization interventions continue to be the cornerstone approach to treatment of CLI, with various results on life expectancy, limb salvage, and wound management.[3] It is estimated that 50% to 90% of patients with CLI will undergo some type of revascularization procedure.[1] The advancement of medical therapies and the effect of high intervention rate limit the understanding of the natural history of CLI. In addition, many patients might present in advanced stages. By then, those patients are not fit for surgical intervention and can be mostly managed conservatively, and their life quality expectancy is not well known.

To aid the Society for Vascular Surgery (SVS) in developing the global clinical practice guidelines, we conducted this systematic review and meta-analysis to synthesize the existing evidence about the natural history of untreated CLI. Our goal is to provide patients and surgeons at the point of decision-making with the best available estimates of clinical outcomes of interest. This information can lead patients to make more informed decisions once they are aware of the natural history of CLI and possible course.

METHODS

The reporting of this systematic review complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[4] in agreement with the methodology for clinical practice guidelines for the management of arteriovenous access.[5] An a priori protocol was developed by the SVS committee on the

From the Division of Preventive, Occupational, and Aerospace Medicine[a] and The Knowledge Synthesis Unit, The Center for Healthcare Delivery,[b] Mayo Clinic, Rochester; and the Division of Vascular and Endovascular Surgery, University of California San Francisco, San Francisco.[c]

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Correspondence: Mohammad Hassan Murad, MD, MPH, Division of Preventive, Occupational and Aerospace Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (e-mail: murad.mohammad@mayo.edu).

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management of CLI and specified the outcomes of interest: (1) mortality, (2) major amputations, and (3) wound healing (better or worse).

Study eligibility. We included original controlled and uncontrolled studies (prospective and retrospective) that enrolled adult patients with CLI or severe limb ischemia (SLI). To be eligible, patients must have rest pain, tissue loss, ulcer, or gangrene; meet the criteria for Rutherford class 4 to 6; or have an ankle pressure <70 mm Hg, toe pressure <50 mm Hg, flat pulse volume recording, or transcutaneous oxygen pressure <40 mm Hg. The patients were diagnosed and observed at least 1 year or longer. We included interventional trials that contributed data only from the placebo or untreated arm.

Literature search. A comprehensive literature search was conducted by an expert reference librarian with input from the study principal investigator (M.H.M.) and SVS committee members. The search included MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, CINAHL, and Scopus. We used a combination of controlled vocabulary and keywords to search for follow-up of untreated or natural history of CLI or SLI. Reviewers working independently and in duplicate identified original eligible studies for further review by screening abstracts and titles. If a study was deemed relevant, the manuscript was obtained and reviewed in full-text version for further assessment. Any inclusion or exclusion disagreements were discussed and reconciled by a third investigator. Previously described data sources, including cited articles and relevant systematic reviews, were searched manually for possible studies, and duplicates were excluded. We expanded the search to include all languages, with last date of inclusion to be November 2014. The detailed search strategy is available in the Appendix (online only).

Data extraction. Two reviewers independently extracted data from each study. We extracted data on patient demographics, characteristics, study design variables, sample size, nonintervention or placebo arms, untreated cases or cohort population, and outcome measures when reported. In addition, for each study, we extracted variables related to CLI or SLI, history of relevant chronic illnesses or comorbidities, and disease-specific effect size, when reported.

Risk of bias assessment. We modified the Newcastle-Ottawa Scale by removing the comparability criteria, which are not applicable for our research question. The risk of bias (quality assessment) focused on cohort selection, outcome ascertainment, and attrition. The untreated arms of interventional studies were considered as case series for quality assessment purposes.

Outcomes. The outcomes of interest were all-cause mortality, major (above-ankle) amputation, and wound or ulcer healing. All-cause mortality was defined as postintervention all-cause mortality measured at ≥1 year of follow-up. Major amputation or limb loss was defined as above-ankle ischemia-related amputation. Wound healing was reported by either improved or worsened ischemia-related wound assessment, when possible.

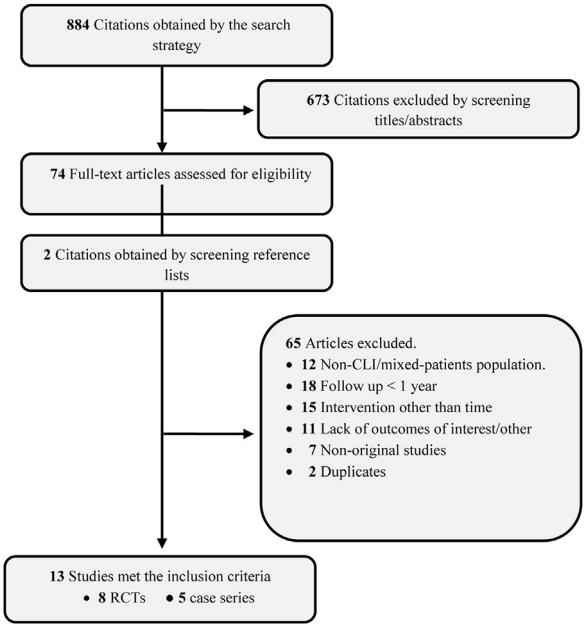

Fig 1. Study selection process. *CLI*, Critical limb ischemia; *RCTs*, randomized controlled trials.

Data synthesis and statistical analysis. We extracted or calculated the rate of outcomes of interest and 95% confidence interval (CI) as estimated by the Jeffreys method.[6] The overall rate (cumulative incidence) was combined using the DerSimonian and Laird random-effects methods after log transforming rates.[7] The I^2 statistic was used to assess heterogeneity of the treatment effect among studies for each outcome. I^2 value >50% and P value < .10 of the Cochrane Q test suggest substantial heterogeneity that is due to real differences in study populations, protocols, interventions, or outcomes. Visual inspection of funnel plots and the Egger linear regression tests were planned to evaluate potential publication bias.[8] All statistical analyses were performed with Stata version 12 (StataCorp, College Park, Tex). We performed subgroup analysis to compare outcomes based on length of follow-up and severity of ischemia and to determine if advances in medical treatment during the last several decades have improved outcomes for those with CLI who received treatments before and after 1997. This was the year atorvastatin was introduced to the marketplace and statin use became increasingly prevalent. The strength of evidence was assessed on the basis of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.[9]

RESULTS

Literature search and included studies. The initial search resulted in 884 citations, in which 74 studies were reviewed in full text by two authors. Thirteen studies

Table I. Characteristics of the included studies

Study (study design)	*Patients (N)/ limbs (n)*	*Follow-up period, months*	*Age, years, mean*	*Male gender, %*	*HTN, %*	*DM, %*	*Smokers, %*	*Inclusion criteria*
Andersen,[10] 1989 (case series)	NR/38	42	62	62	17	8	NR	Patients with digital pressure <30 mm Hg
Boccalon,[11] 2000 (RCT)	207	12	65	NR	NR	28	28	Patients with trophic skin changes (ulcers or gangrene) or rest pain due to severe arterial disease Underlying atherosclerosis requiring the patients to have maximum ankle systolic Doppler pressure ≤70 mm Hg or toe systolic pressure ≤50 mm Hg or less
Belch,[12] 2011 (RCT)	259	12	69	70	82	54	18	CLI with skin lesions (ischemic ulcers or minor gangrene) Objective evidence of CLI, including ankle systolic pressure <70 mm Hg, or toe systolic pressure <50 mm Hg, or $TcPo_2$ <30 mm Hg
Lassila,[13] 1986 (case series)	104	~ 141	61	81	18	15	91	Patients with peripheral artery disease manifested as intermittent claudication, rest pain, or ischemic skin lesions of lower extremities
Lepantalo,[14] 1996 (case series)	105	12	75	45	49	51	NR	Patients with unreconstructed chronic CLI Ankle pressure ≤50 mm Hg or toe pressure ≤30 mm Hg
Marston,[15] 2006 (case series)	142/169	18	71	59	NR	71	84	ABI <0.7 or a toe pressure <50 mm Hg Full-thickness ulcers extending through the entire dermis into subcutaneous tissue present for minimum of 6 weeks
Marston,[16] 2011 (RCT)	24	12	69	67	NR	50	84	Major no-option CLI population
Nikol,[17] 2008 (RCT)	56	13	72	75	85.7	50	NR	Signs of healing of trophic lesions (reduction in ulcer size or depth) were required to be absent for >2 weeks before the first administration of the study drug
Powell,[18] 2008 (RCT)	26	12	71	63	NR	71	83	Patients with inadequate limb perfusion that included ulceration, gangrene, and rest pain due to impaired peripheral blood flow Ankle pressure <70 mm Hg, toe pressure <50 mm Hg, $TcPo_2$ <40 mm Hg
Powell,[19] 2010 (RCT)	6	12	78	33	NR	50	50	Patients with ischemic peripheral ulcer or tissue loss Ankle pressure <70 mm Hg, toe pressure <50 mm Hg, $TcPo_2$ <40 mm Hg
Powell,[20] 2012 (RCT)	24	12	76.3	58	NR	63	38	Patients 18 to 90 years old with a diagnosis of CLI, defined as persistent, recurring ischemic rest pain ≥2 weeks' duration and/or ulceration or gangrene of the toe or foot, with toe systolic pressure ≤50 mm Hg (or absent palpable pedal pulse in patients with diabetes) or ankle systolic pressure ≤70 mm Hg Patients with infrainguinal occlusive disease and deemed amenable to revascularization Controlled blood pressure with or without antihypertensive therapy, and adequate antiplatelet therapy established before randomization Statin therapy was required unless contraindicated

(*Continued on next page*)

Table I. Continued.

Study (study design)	*Patients (N)/ limbs (n)*	*Follow-up period, months*	*Age, years, mean*	*Male gender, %*	*HTN, %*	*DM, %*	*Smokers, %*	*Inclusion criteria*
Brass,[21,a] 2006 (RCT)	190	6-12	69.7	68	NR	53.7	NR	Patients were 40 years old and were able to provide informed consent directly or through an authorized representative CLI clinically defined by the presence of distal extremity pain at rest requiring use of analgesics for at least 2 weeks or the presence of peripheral ischemic ulcers or areas of gangrene Patients must have had hemodynamic evidence of CLI In the case of patients with rest pain only (Fontaine stage III), CLI diagnosis required a highest ankle systolic pressure (posterior tibial or dorsalis pedis) ≤50 mm Hg in the affected limb, toe systolic pressure ≤30 mm Hg, or pedal $TcPo_2$ of ≤30 mm Hg (with a limb/chest $TcPo_2$ ratio ≤0.5) In the case of patients with ulcers or gangrene (Fontaine stage IV), the ankle and toe pressure cutoffs were ≤70 mm Hg and ≤50 mm Hg, respectively
Elgzyri,[22,a] 2013 (case series)	319	24	78	58	NR	100	NR	Individuals with diabetes mellitus and foot ulcer Systolic toe pressure <45 mm Hg, a systolic ankle pressure <80 mm Hg, or, in the case of nonmeasurable pressure levels, nonpalpable foot pulses with an ulcer Wagner grade 4-5 or rest pain All patients fulfilled Fontaine grade 4

ABI, Ankle-brachial index; *CLI,* critical limb ischemia; *DM,* diabetes mellitus; *HTN,* hypertension; *NR,* not reported; *RCT,* randomized controlled trial; *$TcPo_2$,* transcutaneous oxygen pressure.
[a]Studies were not included in the meta-analysis.

Table II. Risk of bias of untreated arms of interventional studies

Study	*Selection of nonexposed cohort*	*Ascertainment of exposure*	*Demonstration that outcome of interest not present at the start of study*	*Assessment of outcome*	*Adequacy of follow-up of cohort*	*Attrition*
Boccalon, 2000	Drawn from same community as exposed cohort	Secure records	Yes	Independent assessment	Yes	Complete follow-up
Belch, 2011	Drawn from same community as exposed cohort	Secure records	Yes	Independent assessment	Yes	Complete follow-up
Marston, 2011	Drawn from same community as exposed cohort	Secure records	Yes	Independent assessment	Yes	Complete follow-up
Nikol, 2008	Drawn from same community as exposed cohort	Secure records	Yes	Independent assessment	Yes	Complete follow-up
Powell, 2008	Drawn from same community as exposed cohort	Secure records	Yes	Independent assessment	Yes	Subjects lost to follow-up, unlikely to introduce bias
Powell, 2010	Drawn from same community as exposed cohort	Secure records	Yes	Independent assessment	Yes	Complete follow-up
Powell, 2012	Drawn from same community as exposed cohort	Secure records	Yes	Independent assessment	Yes	Subjects lost to follow-up, unlikely to introduce bias

Table III. Risk of bias of case series studies

Study assessment criteria	*Andersen, 1989*	*Lassila, 1986*	*Lepantalo, 1996*	*Marston, 2006*
Hypothesis/objective of the study clearly described	No	Yes	Yes	Yes
The inclusion and exclusion criteria are clearly defined	No	Yes	Yes	Yes
Clear definition of the reported outcomes	No	No	No	Yes
Prospective data collection	Yes	No	No	Yes
Consecutive patient selection	No	Yes	Yes	No
Clear description of outcomes	Yes	Yes	Yes	Yes
Outcomes stratified or adjusted for confounders	Yes	Yes	Yes	Yes

Table IV. Outcomes reported in individual studies

		Limb loss		*Ulcer healing*	
Study	*Mortality, %*	*Patients with limb loss, %*	*Limbs lost, %*	*Improved, %*	*Worsening, %*
Lassila, 1986	62	—	—	—	—
Andersen, 1989	28	—	DP, 0-9: 66 DP, 10-19: 38 DP, 20-29: 18	—	—
Lepantalo, 1996	54	—	46	—	—
Boccalon, 2000	12	29	—	10	—
Marston, 2006	—	—	38	—	—
Nikol, 2008	23	34	—	—	—
Powell, 2008	8	—	—	—	—
Powell, 2010	33	16	—	0	—
Marston, 2011	8	—	—	—	46
Belch, 2011	15	21	—	—	—
Powell, 2012	8	25	—	—	50

DP, Digital pressure.

Table V. Meta-analysis results

Outcomes	*Proportion*	*95% CI*	I^2, %	P, *heterogeneity*	P, *between subgroups*
Mortality	0.22	0.12-0.32	94.2	<.001	
≤2 years	0.169	0.08-0.25	90.0	<.001	.10
>2 years	0.45	0.12-0.77	94.7	<.001	
Mortality[a]	0.18	0.10-0.26	89.4	<.001	
≤2 years	0.17	0.08-0.25	90.0	<.001	.12
>2 years	0.28	0.16-0.40	—	—	
Ulcer improved	0.08	0.03-0.13	34.3	.218	
Ulcer worsened	0.35	0.10-0.62	82.6	.017	
Limb loss, No. of patients	0.22	0.02-0.42	95.9	<.001	
Limb loss, No. of legs	0.30	0.19-0.41	85.4	<.001	
≤2 years	0.28	0.16-0.40	86.7	<.001	.21
>2 years	0.396	0.26-0.52	—	—	

CI, Confidence interval.
[a]Excluding Lassila et al[13] (follow-up time was markedly longer than that of others studies).

eventually met the eligibility criteria and were included in this systematic review, but only 11 studies were included in the meta-analysis as show in Fig 1. The characteristics of included studies are summarized in Table I. Eight of the included studies were noninterventional or placebo arms of randomized controlled trials; five studies were case series. Tables II and III include the risk of bias assessment of the included studies. Results of outcomes of individual studies are shown in Table IV. The median length of follow-up was 12 months (range, 12-141 months).

Meta-analysis. The all-cause mortality cumulative incidence was 0.22 (95% CI, 0.12-0.32), as shown in Table V. Most of the studies had follow-up of 12 to 18 months. However, Lassila et al[13] reported outcomes at a 141-month average follow-up period. When this study was excluded, the all-cause mortality cumulative risk was 0.18 (95% CI, 0.10-0.26), as shown in Fig 2. Subgroup analysis was performed on those studies of >2 years or <2 years of follow-up duration; this showed no significant difference, even when higher rates were reported

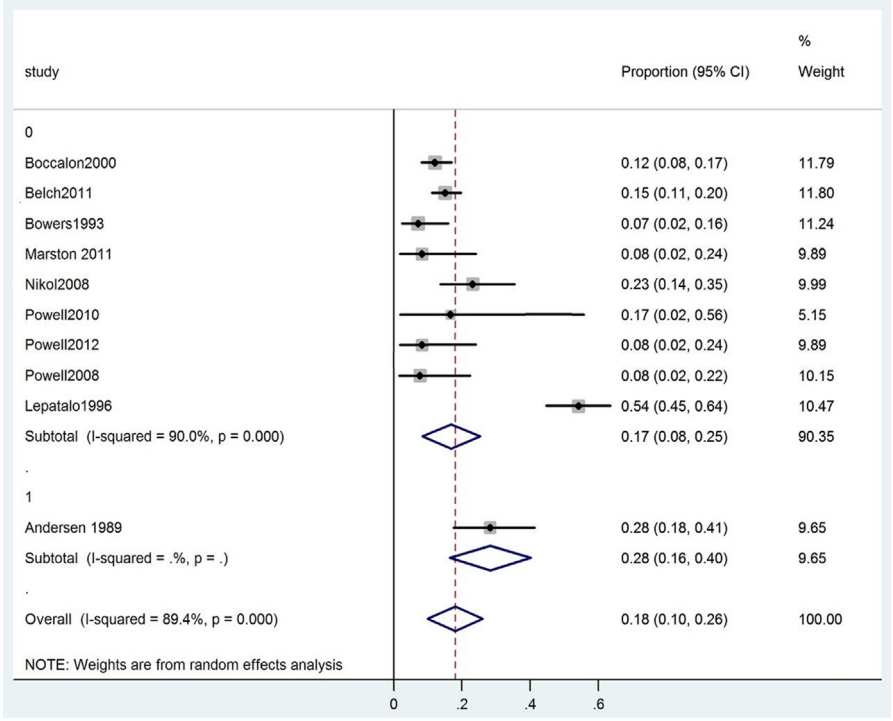

Fig 2. Meta-analysis of mortality in patients of untreated critical limb ischemia (CLI) with follow-up ≤2 years (0) and >2 years (1) (excluding Lassila et al[12]). *CI,* Confidence interval.

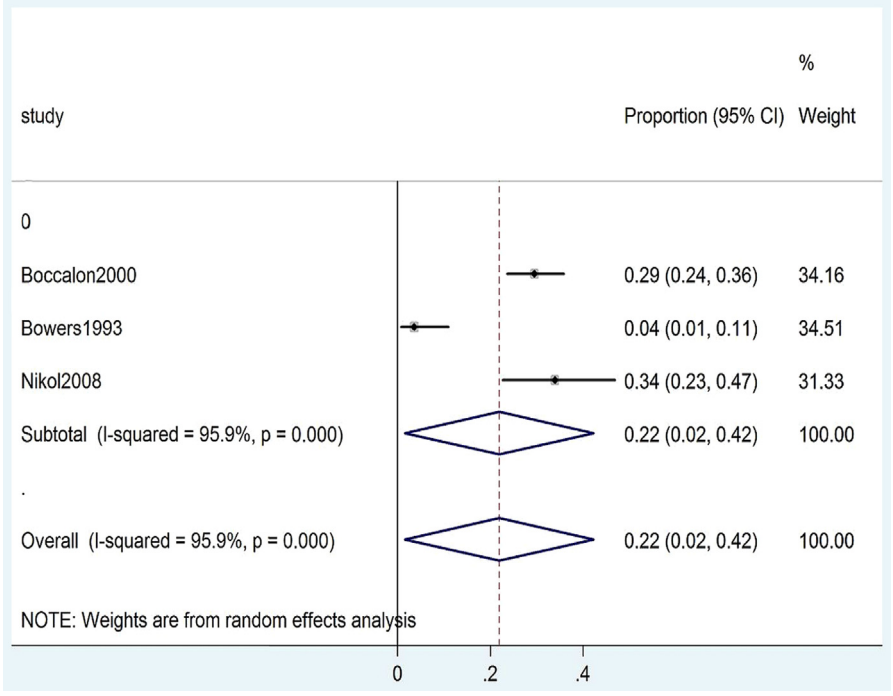

Fig 3. Meta-analysis of limb loss (unit of analysis = number of patients) in patients of untreated critical limb ischemia (CLI) with follow-up ≤2 years (0) and >2 years (1). *CI,* Confidence interval.

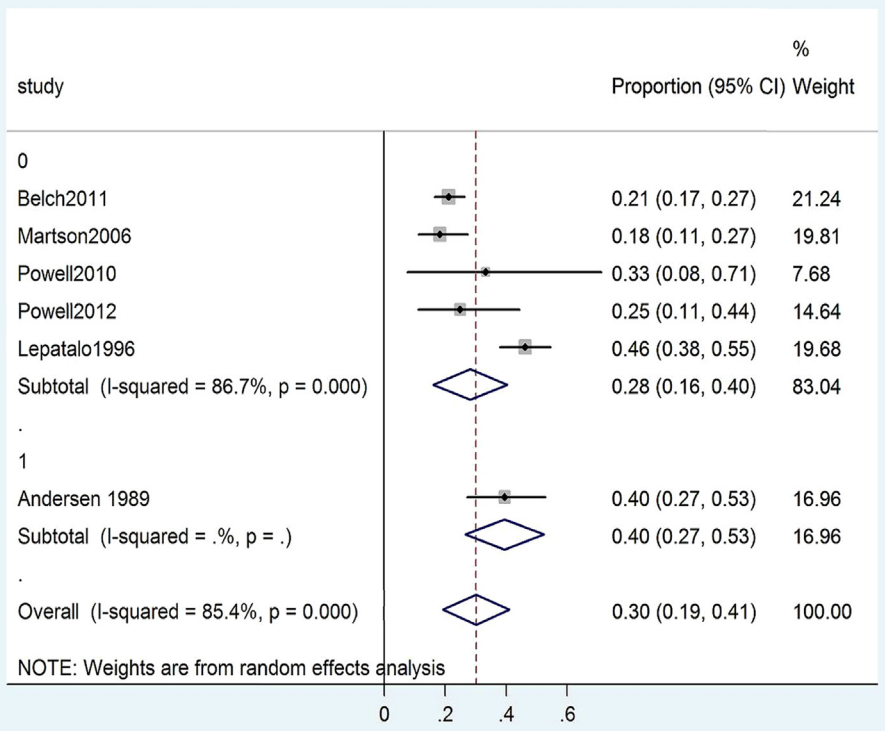

Fig 4. Meta-analysis of limb loss (unit of analysis = number of limbs) in patients of untreated critical limb ischemia (CLI) with follow-up ≤2 years (0) and >2 years (1). *CI,* Confidence interval.

with longer follow-up studies ($P = .10$), as shown in Table V.

The overall cumulative incidence of patients with major amputation was 0.22 (95% CI, 0.02-0.42), as shown in Fig 3. In considering analysis per limb (vs per patient), the cumulative incidence was 0.30 (95% CI, 0.19-0.41), as shown in Fig 4. A subgroup analysis excluding Andersen et al,[10] a study that has a longer duration of follow-up, did not significantly change the overall estimate in comparison (Table V). Similar to mortality, the same trend was seen in limb loss, with higher rates in those studies that reported outcomes for >2 years of follow-up, but such a trend was not statistically significant ($P = .21$).

Ulcer or wound improvement or worsening was reported in four studies (Table IV). Two studies[11,19] reported on ulcer improvement, and the cumulative incidence of improvement was 0.08 (95% CI, 0.03-0.13), as shown in Fig 5. Two studies[16,20] reported on ulcer worsening, with a cumulative incidence of 0.35 (95% CI, 0.10-0.62), as shown in Fig 6. Complete healing was not evidently reported, and therefore it was not possible to include it as an outcome.

Relevant comorbidities, such as diabetes and hypertension, were not consistently reported, and related stratified or subgroup analyses were not possible. One study, however, did show a significant increase in mortality, but not amputation, in patients with diabetes.[14] One study[10] showed increasing rates of limb loss as distal toe pressure decreased. Most studies reported ancillary treatments generically as "standard treatment" and did not specifically describe the type of treatments (anticoagulants, antihypertensives, pain management, or lipid-lowering medications). There were insufficient data about predictors of outcomes, including gender, race, and if they received any imaging, to determine eligibility for revascularization treatment.

Regression analysis to assess the difference between outcomes before and after year 1997 showed a significant effect for mortality (coefficient, −0.25; 95% CI, −0.47 to −0.22) as well as for limb loss (coefficient, −0.24; 95% CI, −0.35 to −0.12), suggesting improved outcomes in recent times after 1997. The strength of evidence supporting the meta-analytic estimates was low, mainly because of the serious risk of bias, inconsistency (high heterogeneity between studies), and imprecision. Forest plots for these analyses are depicted in Figs 2-6.

Some studies[21,22] were not included in the quantitative analysis; there was disagreement of criteria defining CLI with our protocol (or inclusion of a mixed population), or the studies did not report clear distinction in their inclusion criteria to assess their eligibility in our quantitative analysis because the outcomes of interest were not reported clearly at or beyond 1 year.[21,22] Therefore, the consensus was to include these studies in the systematic review only but not in the meta-analysis.

The Circulase trial reported 10.5% amputation rate and 24.5% ulcer-free patients by the 6-month follow-up period and 10% all-cause mortality rate by the end of the trial

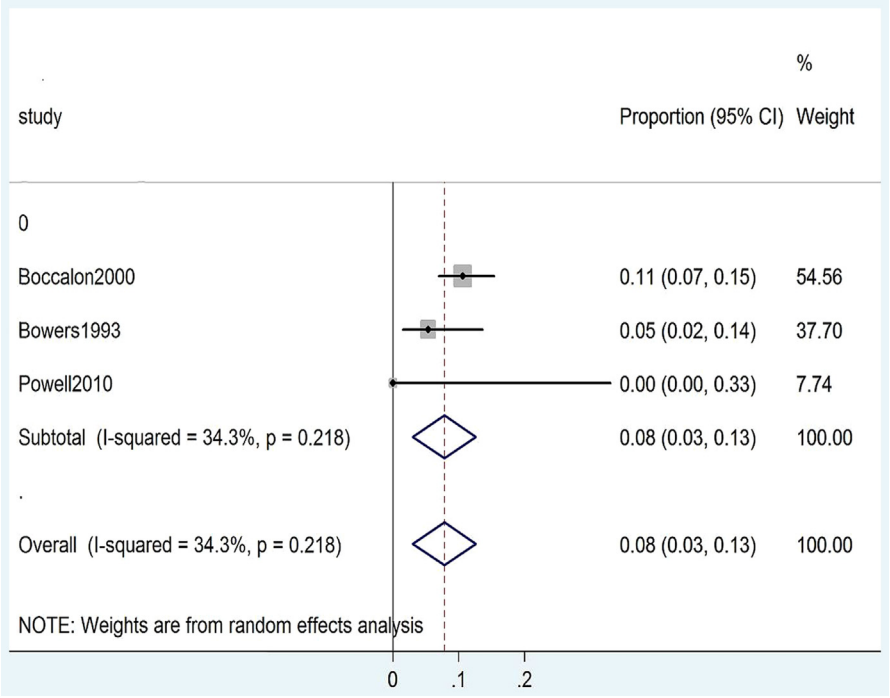

Fig 5. Meta-analysis of ulcer or wound improvement in patients of untreated critical limb ischemia (CLI) with follow-up ≤2 years (0) and >2 years (1). *CI,* Confidence interval.

while following up 181 patients with CLI who received placebo.[21]

Elgzyri et al[22] observed 602 patients between 1 and 276 weeks and found that 30% to 50% healed either primarily (76%) or with a minor amputation (24%). Seventeen percent of patients healed after major amputation, and 33% died unhealed.

We attempted to report findings about primary outcomes in accordance with the SVS Lower Extremity Threatened Limb Classification System,[23] looking into wound description or classification, ischemia, and other factors including symptom improvement and neuropathy. However, such data were not reported sufficiently or accordingly and therefore were not included.

DISCUSSION

We conducted a systematic review and meta-analysis examining the mortality, limb loss, and wound healing in patients with untreated CLI. There was a high rate of mortality and limb loss associated with CLI (almost one in five patients during a median follow-up of 1 year). Wounds or ulcers were more likely to worsen. There is evidence that advances in medical treatment have improved outcomes after 1997.

Determining the natural history of CLI is inherently difficult because of the high rate of intervention and high rate of outcomes of interest. Further research on untreated CLI is unlikely and naturally unethical. Numerous studies report the effectiveness of medical as well as of surgical interventions. The medical treatments range from the use of agents such as prostacyclin, hydroxyethylrutoside, and warfarin to bone marrow mononuclear cell, non-viral 1 fibroblast growth factor, and hepatocyte growth factor gene therapy. These medical therapies report varying degrees of effectiveness.[12,17-20,24-34] Angioplasty, with or without stenting, and bypass surgery are widely used surgical interventions and report tangible results on decreasing mortality and limb loss while also increasing patency and improving wound healing.[35-43] The literature of CLI is difficult to interpret as some studies do not clearly describe the diagnostic criteria or fail to adhere to accepted criteria for CLI, such as those put forth by the TransAtlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II).[1] In addition, studies failed to report their findings in accordance with the SVS Lower Extremity Threatened Limb Classification System,[23] which limits the interpretation of more findings. The natural history in patients with CLI could not be observed without its own level of bias. Heterogeneity between studies was high because of the different design of studies as the inclusion criteria of the eligible studies varied. The observed population is usually chosen because they were unfit to receive treatments for various reasons. Even when treated conservatively, many patients have received undefined ancillary treatments, and those treatments might affect the course of evolution and progress (ie, natural history) of CLI. Whereas this might limit our results, our exhaustive search, rigorous methodology, and adherence to the TASC II definition of CLI warrant the importance of these findings. Overall,

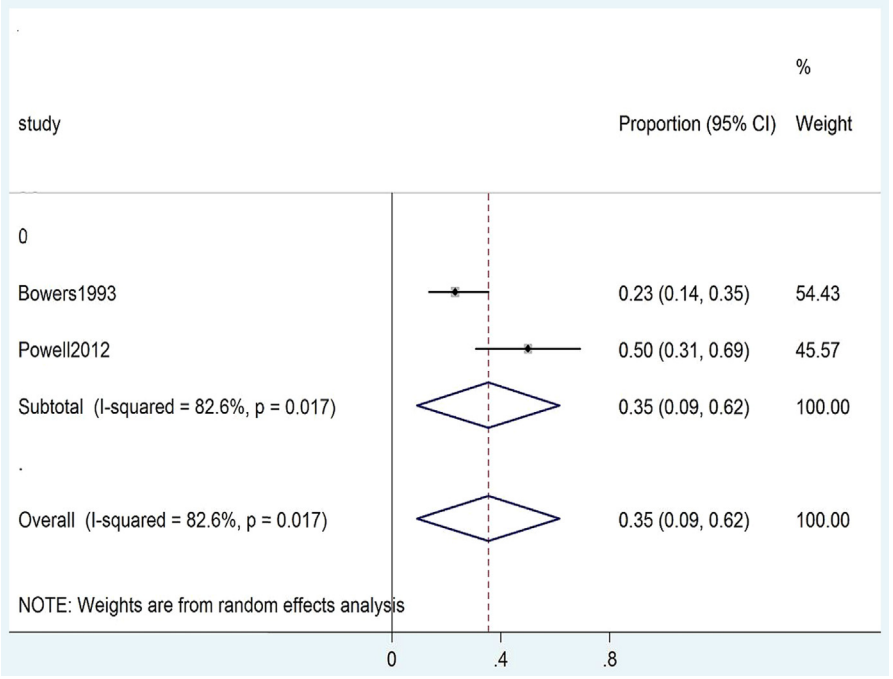

Fig 6. Meta-analysis of ulcer or wound worsening in patients of untreated critical limb ischemia (CLI) with follow-up ≤2 years (0) and >2 years (1). *CI,* Confidence interval.

the observed mortality and amputation rates (per persons or per limbs) are consistent with reports from the TASC II.[1] Such findings demonstrate the need for effective prevention and early treatment of CLI.

CONCLUSIONS

Mortality and major amputations are common in patients who have untreated CLI, although these outcomes have been shown to be improved over the course of time. Although the exact reason for improvement is unclear, it is likely related to improved medical care for patients with CLI as well as improved clinical care of the comorbidities associated or existing with CLI.

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AUTHOR CONTRIBUTIONS

Conception and design: MC, MM
Analysis and interpretation: AAD, MS, ZW, MC, MM
Data collection: AAD, MS, NA, CU, ME
Writing the article: AAD, MS, CU, ZW, MC, MM
Critical revision of the article: AAD, MS, NA, CU, ZW, ME, MC, MM
Final approval of the article: AAD, MS, NA, CU, ZW, ME, MC, MM
Statistical analysis: AAD, MS
Obtained funding: AAD, MS, MM
Overall responsibility: MM

AAD and MS contributed equally to this article and share co-first authorship.

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Additional material for this article may be found online at www.jvascsurg.org.

APPENDIX (online only).

Search strategy

Ovid. Database(s): Embase 1988 to 2012 Week 45, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews—Cochrane Central Register of Controlled Trials November 2012, EBM Reviews—Cochrane Database of Systematic Reviews 2005 to October 2012.

#	*Searches*	*Results*
1	exp Ischemia/	455099
2	exp peripheral occlusive artery disease/	87444
3	exp Peripheral Vascular Diseases/	949166
4	exp Atherosclerosis/	143600
5	exp arteriosclerosis/	272164
6	exp intermittent claudication/	13287
7	exp Arterial Occlusive Diseases/	264156
8	(ischemia or ischaemia or ischemic or ischaemic or "circulation disorder*" or "circulation failure*" or "circulation disturbance*" or "circulatory disorder*" or "circulatory failure*" or "circulatory disturbance*" or ((arter* or vascul* or vein or veno or peripheral*) adj2 (steno* or lesio* or block* or occlus* or obliterat* or insufficiency or obstruct*)) or "peripheral arterial disease*" or "peripheral artery disease*" or "peripheral occlusive disease*" or "peripheral angiopath*" or PVD or PAOD or atherosclero* or atherogenesis or atheroma* or "peripheral vascular disease*" or (intermitten* adj claudicat*) or arteriosclor* or CLI).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui, tx, ct]	1164002
9	or/1-8	1686866
10	exp Leg/	156814
11	exp Leg Ulcer/	24965
12	exp lower extremity/	227433
13	(leg or legs or foot or feet or toe or toes or knee* or ankle* or thigh* or calf or "calfs lower limb*" or "lower extremit*" or buttock* or hip or hips).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui, tx, ct]	969663
14	or/10-13	976186
15	9 and 14	110003
16	exp Survival Analysis/ or exp Survival/ or exp Survival Rate/	757206
17	exp Wound Healing/	167661
18	exp amputation/	38931
19	(survival or (heal* adj3 (wound* or injur*)) or (limb* adj3 (loss or lose or losing)) or amputat*).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui, tx, ct]	1767030
20	or/16-19	1842602
21	exp placebo/	174413
22	exp Placebo Effect/ or exp Placebos/	230707
23	(untreated or placebo or "natural history").mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui, tx, ct]	831231
24	21 or 22 or 23	851772
25	15 and 20 and 24	1329
26	exp controlled study/	3970792
27	exp evidence based medicine/	608047
28	evidence-based.mp.	205557
29	((control$ or randomized) adj2 (study or studies or trial or trials)).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui, tx, ct]	5088223
30	meta analysis/	104758
31	meta-analys$.mp.	168542
32	exp "systematic review"/	54429
33	(systematic* adj review$).mp.	128076
34	exp Guideline/ or exp Practice Guideline/	303328
35	guideline$.ti.	97111
36	or/26-35	5685384
37	exp case study/	1624994
38	follow up studies/	1113321
39	exp Cohort Studies/	1459705
40	exp longitudinal study/	947302
41	exp retrospective study/	727324
42	exp prospective study/	604110

(*Continued on next page*)

Continued.

#	*Searches*	*Results*
43	exp observational study/	34071
44	exp comparative study/	2347880
45	exp clinical trial/	1602744
46	exp evaluation/	1162931
47	exp twins/	42883
48	exp validation study/	36356
49	exp experimental study/ or exp field study/ or in vivo study/ or exp panel study/ or exp pilot study/ or exp prevention study/ or exp quasi experimental study/ or exp replication study/ or exp theoretical study/ or exp trend study/ or clinical study/	1543507
50	((clinical or evaluation or twin or validation or experimental or field or "in vivo" or panel or pilot or prevention or replication or theoretical or trend or comparative or cohort or longitudinal or retrospective or prospective or population or concurrent or incidence or follow-up or observational or multivariate) adj (study or studies or survey or surveys or analysis or analyses or trial or trials)).mp.	7571118
51	("case study" or "case series" or "clinical series" or "case studies").mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui, tx, ct]	180052
52	or/37-51	11000007
53	36 or 52	14115611
54	25 and 53	1166
55	from 25 keep 830-1113	284
56	limit 55 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or twin study or validation studies) [Limit not valid in Embase,CCTR,CDSR; records were retained]	142
57	54 or 56	1166
58	animals/	6052994
59	humans/	24016629
60	58 not 59	4369940
61	57 not 60	1162
62	limit 61 to (book or book series or editorial or erratum or letter or note or addresses or autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	154
63	61 not 62	1008
64	from 25 keep 1114-1329	216
65	63 or 64	1147
66	remove duplicates from 65	903

Scopus.

1 TITLE-ABS-KEY(ischemia or ischaemia or ischemic or ischaemic or "circulation disorder*" or "circulation failure*" or "circulation disturbance*" or "circulatory disorder*" or "circulatory failure*" or "circulatory disturbance*" or (arter* W/2 steno*) or (arter* W/2 lesio*) or (arter* W/2 block*) or (arter* W/2 occlus*) or (arter* W/2 obliterat*) or (arter* W/2 insufficiency) or (arter* W/2 obstruct*) or (vascul* W/2 steno*) or (vascul* W/2 lesio*) or (vascul* W/2 block*) or (vascul* W/2 occlus*) or (vascul* W/2 obliterat*) or (vascul* W/2 insufficiency) or (vascul* W/2 obstruct*) or (vein W/2 steno*) or (vein W/2 lesio*) or (vein W/2 block*) or (vein W/2 occlus*) or (vein W/2 obliterat*) or (vein W/2 insufficiency) or (vein W/2 obstruct*) or (veno W/2 steno*) or (veno W/2 lesio*) or (veno W/2 block*) or (veno W/2 occlus*) or (veno W/2 obliterat*) or (veno W/2 insufficiency) or (veno W/2 obstruct*) or (peripheral* W/2 steno*) or (peripheral* W/2 lesio*) or (peripheral* W/2 block*) or (peripheral* W/2 occlus*) or (peripheral* W/2 obliterat*) or (peripheral* W/2 insufficiency) or (peripheral* W/2 obstruct*) or "peripheral arterial disease*" or "peripheral artery disease*" or "peripheral occlusive disease*" or "peripheral angiopath*" or PVD or PAOD or atherosclero* or atherogenesis or atheroma* or "peripheral vascular disease*" or (intermitten* W/1 claudicat*) or arteriosclor* or CLI)

2 TITLE-ABS-KEY(leg or legs or foot or feet or toe or toes or knee* or ankle* or thigh* or calf or calfs "lower limb*" or "lower extremit*" or buttock* or hip or hips)

3 TITLE-ABS-KEY(survival or (heal* W/3 wound*) or (heal* W/3 injur*) or (limb* W/3 loss) or (limb* W/3 lose) or (limb* W/3 losing) or amputat*)

4 TITLE-ABS-KEY(untreated or placebo or "natural history")

5 TITLE-ABS-KEY("comparative study" OR "comparative survey" OR "comparative analysis" OR "cohort study" OR "cohort survey" OR "cohort analysis" OR "longitudinal study" OR "longitudinal survey" OR "longitudinal analysis" OR "retrospective study" OR "retrospective survey" or "retrospective analysis" OR "prospective study" OR "prospective survey" OR "prospective analysis" OR "population study" OR "population survey" OR "population analysis" OR "concurrent study" OR "concurrent survey" OR "concurrent analysis" or "incidence study" OR "incidence survey" OR "incidence analysis" OR "follow-up study" OR "follow-up survey" OR "follow-up analysis" or "observational study" OR "observational survey" OR "observational analysis" OR "case study" OR "case series" OR "clinical series" OR "case studies" or "clinical study" OR "clinical trial" or "evaluation study" OR "evaluation survey" OR "evaluation analysis" or "twin study" OR "twin survey" OR "twin analysis" or "validation study" OR "validation survey" OR "validation analysis" or "experimental study" OR "experimental analysis" or "field study" OR "field survey" OR "field analysis" or "in vivo study" OR "in vivo analysis" or "panel study" OR "panel survey" OR "panel analysis" or "pilot study" OR "pilot survey" OR "pilot analysis" or "prevention study" OR "prevention survey" OR "prevention analysis" or "replication study" OR "replication analysis" or "theoretical study" OR "theoretical analysis" or "trend study" OR "trend survey" OR "trend analysis" or (evidence W/1 based) OR (meta W/1 analys*) OR (systematic* W/2 review*) OR guideline OR (control* W/2 stud*) OR (control* W/2 trial*) OR (randomized W/2 stud*) OR (randomized W/2 trial*))

6 1 and 2 and 3 and 4 and 5

7 PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)

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10 8 and not 9