Bypass surgery versus endovascular interventions in severe or critical limb ischemia

Abd Moain Abu Dabrh, MBBCh, MS,[a,b] Mark W. Steffen, MD, MPH,[a] Noor Asi, MD,[b] Chaitanya Undavalli, MBBS,[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 is associated with a significant morbidity and mortality. We systematically reviewed the evidence to compare bypass surgery with endovascular revascularization in patients with critical limb ischemia.**
Methods: **We systematically searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials, CINAHL, and Scopus through October 2014 for comparative studies (randomized and nonrandomized). Predefined outcomes of interest were mortality, major amputation, patency, and wound healing. We pooled odds ratios (ORs) of the outcomes of interest using the random-effects model.**
Results: **Nine studies that enrolled 3071 subjects were included. There was no significant difference in mortality (OR, 0.72; 95% confidence interval [CI], 0.44-1.16) or amputation (OR, 1.2; 95% CI, 0.87-1.65). Bypass surgery was associated with higher primary patency (OR, 2.50; 95% CI, 1.25-4.99) and assisted primary patency (OR, 3.39; 95% CI, 1.53-7.51). The quality of evidence was low for mortality and amputation outcomes and moderate for patency outcomes.**
Conclusions: **Low quality of evidence due to imprecision and heterogeneity suggests that bypass surgery and endovascular approaches may have similar effect on mortality and major amputations. However, better primary and primary assisted patency can be expected with surgery. (J Vasc Surg 2016;63:244-53.)**

It is estimated that 5% to 10% of patients with peripheral artery disease older than 50 years develop severe or critical limb ischemia (CLI) within 5 years.[1] The incidence in the United States and Europe ranges between 500 and1000 cases per million.[2] Bypass surgery and more recently endovascular interventions with angioplasty and stenting have become the treatment of choice. Endovascular interventions are thought to carry lower risk of morbidity and mortality, but the risk of procedural failure may be higher compared with bypass surgery.[3] Advances in both approaches have markedly lowered such risk and improved outcomes.

Several observational and clinical trials have been published comparing bypass and endovascular interventions. The TransAtlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) recommends revascularization as the optimal treatment for patients with CLI,[1] but the type of revascularization for patients with CLI remains a subject of debate. In 2011, the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines created a focused update on management of CLI mainly driven by the results of the Bypass Versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial and concluded different recommendations.[4,5] The evidence comparing the effect of these two main interventions on mortality, morbidity, and limb function remains inconclusive.

We conducted a systematic review and meta-analysis to synthesize the evidence about the effect of bypass surgery vs endovascular revascularization on all-cause mortality, limb loss (major amputation), patency, and wound healing in patients with CLI. The review compared controlled studies that enrolled patients with critical or severe limb ischemia with a follow-up of ≥1 year.

METHODS

The reporting of this systematic review follows the statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[6] in agreement with the methodology for clinical practice guidelines for the management of arteriovenous access.[7]

Study eligibility. We limited our inclusion criteria to original longitudinal and controlled (randomized and

From the Division of Preventive, Occupational, and Aerospace Medicine[a] and 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]
This article was partially funded by the Society for Vascular Surgery.
Author conflict of interest: none.
Additional material for this article may be found online at www.jvascsurg.org.
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).
The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.
0741-5214

http://dx.doi.org/10.1016/j.jvs.2015.07.068

nonrandomized) studies that enrolled adult patients with critical or severe limb ischemia with follow-up of ≥1 year. Studies had to be comparative (ie, endovascular approaches vs bypass surgery) and to have enrolled patients with critical or severe limb ischemia. Critical or severe limb ischemia-eligible patients were defined by the following criteria: patients who have rest pain, tissue loss, ulcer, or gangrene; meet the Rutherford criteria for class 4 to 6; or have ankle pressure <70 mm Hg, toe pressure <50 mm Hg, flat pulse volume recording, or transcutaneous oxygen pressure <40 mm Hg at the time of diagnosis. Endovascular revascularization treatments included percutaneous transluminal angioplasty and stenting.

Literature search. A comprehensive literature search was conducted by an expert reference librarian with input from the study principal investigator as shown in the Appendix (online only). The search included the electronic databases MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, CINAHL, and Scopus, using various combinations of controlled vocabulary supplemented with keywords to search for studies of revascularization of critical or severe limb ischemia.

Reviewers working independently identified original studies eligible for further review by screening abstracts and titles in duplicates method. 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 the senior investigators. Previously described data sources, including citing articles and relevant systematic reviews, were searched manually for possible studies, and duplicates were excluded. We expanded our search to include all languages, with the last date of inclusion to be October 2014.

Data extraction. Two reviewers independently extracted data from each study. We extracted data on patient demographics, baseline characteristics, study design variables, sample size, description of interventions, and outcome measures. In addition, for each study, we extracted variables related to the definition of critical or severe limb ischemia and history of relevant chronic illnesses.

Risk of bias assessment. For cohort studies, we used the Newcastle-Ottawa Scale[8] to appraise the risk of bias (study quality). For randomized clinical trials (RCTs), we used the Cochrane risk of bias tools.[9]

Assessed outcomes. The outcomes of interest reported in eligible studies were all-cause mortality, major amputation or limb loss, patency, and wound healing. Major amputations were defined as above-ankle, ischemia-related amputations. Analysis of major amputations was repeated per limb and per patients. Patency was defined as described in Diehm et al.[10] Primary patency implies patency after the procedure being evaluated. Assisted primary patency refers to when a revision has to be applied to prevent occlusion or progression of stenosis, and this was reported only in Dosluoglu et al.[11] Secondary patency refers to patency of the initially treated vessel after a reintervention to restore patency after occlusion. Wound healing was reported by either improved or worsened ischemia-related wound assessment, when possible. We planned an a priori hypothesis to stratify outcomes in accordance with the Society for Vascular Surgery (SVS) Lower Extremity Threatened Limb Classification System.[12]

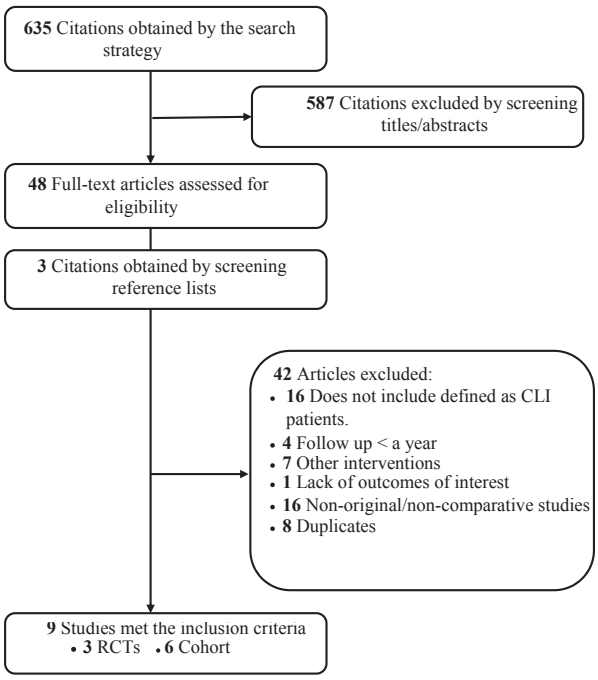


Fig 1. Flowchart shows the selection process of eligible studies. *CLI,* Critical limb ischemia; *RCTs,* randomized clinical trials.

Data synthesis and statistical analysis. We pooled odds ratios (ORs) of the outcomes of interest using the DerSimonian and Laird random-effects model,[13] with heterogeneity estimated by the Mantel-Haenszel method. OR < 1.0 implies lower risk of the outcome with bypass surgery (in comparison with the endovascular approach).

We planned several subgroup analyses a priori on the basis of (1) CLI diagnosis method, that is, hemodynamic criteria vs mixed criteria (ie, hemodynamic or clinical),[14] (2) outcome description (end points according to the SVS Lower Extremity Threatened Limb Classification System),[12] (3) study design (RCT vs observational study), and (4) number of study centers (single-center vs multicenter experience).

Because of the small number of the included studies, we were unable to assess publication bias. We assessed overall heterogeneity across the included studies using the I^2 statistic and Cochran Q test, where I^2 >50% or a conservative P value < .10 suggests high heterogeneity. Stata version 12.1 (StataCorp, College Park, Tex) was used in all statistical analyses.

RESULTS

The initial search resulted in 635 publications. Three additional articles were identified from the bibliography of

Table I. Baseline characteristics of the included studies

Study	*No. of patients*	*Age, years, mean*	*Male gender, %*	*Follow-up, months*	*HTN, %; DM, %*	*Current smokers, %*	*Setting*	*Inclusion criteria*
Ah Chong,[17] 2009 (cohort)	464	74-77	NR	60	79; 70	65	Single center	• Patients with CLI who underwent infrainguinal percutaneous transluminal angioplasty first; or • Infrainguinal bypass surgery
Bergan,[15] 1992 (RCT)	263	61	100	48	51; 29	79	Multicenter	• Intermittent claudication at <2 blocks, rest pain, impending gangrene, ABI <0.90, arterial stenosis of <80% diameter reduction • No contraindication to heparin therapy
Bradbury,[5] 2010 (RCT)	452	NR	59	84	61; 58	32	Multicenter	• Patients with ischemic rest and/or night pain (requiring opiate analgesia) and/or tissue loss (ulcer and/or gangrene) of presumed arterial etiology (regardless of ankle pressure) present for >2 weeks
Dick,[18] 2007 (cohort)	383	75	57	12	75; 50	53	Single center	• Rest pain >2 weeks or ischemic tissue loss; • Ankle pressure <50 mm Hg or toe pressure <30 mm Hg; and • No acute limb ischemia
Dorigo,[19] 2009 (cohort)	73	73	70	12	87; 43	63	Single center	• Patients with PAD and confirmed diagnosis of CLI
Dosluoglu,[11] 2008 (cohort)	127	69	NR	72	78; 58	NR	Single center	• Patients with symptomatic CLI (Rutherford class 3-6)
Korhonen,[20] 2011 (cohort)	858	NR	55	18	73; NR	NR	Single center	• Patients who underwent femoropopliteal revascularization for CLI
Timaran,[21] 2003 (cohort)	188	59	NR	60	71; 26	85	Single center	• All patients with evidence of chronic limb ischemia, excluding TASC type A and type D iliac lesions
Wolf,[16] 1993 (RCT)	263	62	100	48	NR; 29	78	Multicenter	• Male patients with symptomatic PAD • CLI of category 2-5 according to the criteria of the Society for Vascular Surgery and the International Society of Cardiovascular Surgery

ABI, Ankle-brachial index; *DM,* diabetes mellitus; *HTN,* hypertension; *NR,* not reported; *PAD,* peripheral artery disease; *RCT,* randomized clinical trial; *TASC,* TransAtlantic Inter-Society Consensus.

the included articles. Eventually, nine studies enrolling 3071 patients were included. The selection process is shown in Fig 1. Three of the included studies were RCTs[5,15,16] and six were cohort studies.[17-21] Most of the studies were completed in the last 10 years. Two of the RCTs[15,16] were completed in the early 1990s. Four studies[11,17,19,20] reported outcomes for multiple follow-up periods. Follow-up ranged from 1 to 7 years. The characteristics of included studies and results of quality assessment are shown in Tables I and II, respectively. There were significant differences between the studies as to the inclusion criteria particularly in regard to lesion type and location.

Tables III and IV show reported outcomes from individual studies. Table V summarizes the results of overall meta-analysis and subgroup analyses. Table VI presents outcome data stratified by length of follow-up.

Mortality was assessed in all but two trials.[16,21] There was no statistically significant difference in mortality based

Table II. A, Risk of bias assessment

Quality assessment of the included RCTs

Study	*Random sequence generation*	*Allocation concealment*	*Blinding*	*Attrition*	*Selective outcome reporting*
Bergan, 1992	Stratification by site of treatment and symptoms	Not reported	Not reported	11%; in addition, 20 PTA patients were excluded from the analysis without explanation. Report of analysis did not justify such a method and is likely to introduce clinically relevant bias. No ITT analysis was presented.	Outcomes were not explicitly mentioned and were referred to as reporting "adverse systemic effects." There is no substantial justification to why specific outcomes are reported to be significant when they are not.
Wolf, 1993	Randomization was stratified by center and for each of four disease categories. This produced a 2 × 2 × 2 factorial randomization scheme.	Not reported	Not blinded	About 45%	The study prespecified reporting outcomes in subgroups (claudication vs rest pain; iliac vs femoral), but incomplete report of those outcomes is noticed (eg, ABI measurements). In addition, mortality outcome was not reported.
Bradbury, 2010	Randomization by stratification into center, then clinical presentation and ankle pressure into four groups	Allocation concealed (sealed envelopes)	Data analysts, trial managers, and outcome assessors were blinded.	0.8%, which was unlikely to introduce any bias. ITT analysis was reported.	Prespecified outcomes were reported.

Quality assessment of the included cohort studies

Study	*Representativeness of the exposed cohort*	*Selection of the nonexposed cohort*	*Ascertainment of exposure*	*Outcome of interest was* not *present*	*Comparable cohorts*	*Assessment of outcome*
Timaran, 2003	Truly representative	Drawn from the same community	Secure records	Yes	Study controls for most important factor	Record linkage
Dick, 2007	Truly representative	Drawn from the same community	Secure records	Yes	Study controls for most important factor	Record linkage
Dosluoglu, 2008	Somewhat representative	Drawn from the same community	Secure records	Yes	No attempt to control for confounding	Record linkage
Ah Chong, 2009	Truly representative	Drawn from the same community	Secure records	Yes	Study controls for most important factor	Independent blind assessment
Dorigo, 2009	Truly representative	Drawn from the same community	Secure records	Yes	Study controls for most important factor	Record linkage
Korhonen, 2011	Truly representative	Drawn from the same community	Structured interview	Yes	Study controls for most important factor	Record linkage

ABI, Ankle-brachial index; *ITT,* intention to treat; *PTA,* percutaneous transluminal angioplasty; *RCTs,* randomized clinical trials.

on the longest study follow-up (OR, 0.72; 95% confidence interval [CI], 0.44-1.16), as shown in Fig 2. There was no significant difference (interaction) in subgroup analysis based on CLI definition criteria (hemodynamic vs mixed). Studies reporting single-center experience and nonrandomized studies reported lower mortality with bypass compared with the endovascular approach.

Amputation risk did not significantly differ between the two interventions (OR, 1.2; 95% CI, 0.87-1.65), as shown in Fig 3. Studies reporting single-center experience and nonrandomized studies reported lower amputation rate with bypass compared with the endovascular approach. There was no significant difference based on CLI definition criteria. Only two studies reported the number of limbs lost (ie, analysis per limb); bypass surgery had lower risk of limb loss than the endovascular approach (OR, 0.69; 95% CI, 0.46-1.01).

Overall, bypass surgery had higher primary patency (OR, 2.50; 95% CI, 1.25-4.99; Fig 4) and assisted primary patency (OR, 3.39; 95% CI, 1.53-7.51), with no difference

Table II. B, Designated risk of bias of included randomized clinical trials (RCTs)

Study	*Random sequence generation*	*Allocation concealment*	*Blinding*	*Incomplete outcome data*	*Selective outcome reporting*
Bergan, 1992	+	?	?	+	?
Wolf, 1993	+	?	−	−	−
Bradbury, 2010	+	+	+	+	+

High risk, −; unclear, ?; low risk, +.

Table III. Results of individual studies (bypass surgery)

		Limb loss[a]		*Patency*[a]		
Study	*Mortality,*[a] *%*	*Patients with limb loss, %*	*No. of actual limbs lost*	*Primary patency, %*	*Assisted primary patency, %*	*Secondary patency, %*
Bergan, 1992	32	16	NR	NR	NR	NR
Wolf, 1993	NR	10	NR	22	NR	NR
Timaran, 2003	NR	NR	NR	87	NR	NR
Dick, 2007	22	15	NR	NR	NR	NR
Dosluoglu, 2008	26	NR	2	41	41	46
Ah Chong, 2009	49	24	NR	48	NR	58
Dorigo, 2009	13	13	NR	67	51	82
Korhonen, 2011	43	52	40	NR	NR	9
Bradbury, 2010	57	9	NR	NR	NR	NR

NR, Not reported.
[a]Results are based on the latest reported follow-up period per outcome.

Table IV. Results of individual studies (endovascular approach)

		Limb loss[a]		*Patency*[a]		
Study	*Mortality,*[a] *%*	*Patients with limb loss, %*	*No. of actual limbs lost*	*Primary patency, %*	*Assisted primary patency, %*	*Secondary patency, %*
Bergan, 1992	21	6	NR	NR	NR	NR
Wolf, 1993	NR	5	NR	21	NR	NR
Timaran, 2003	NR	NR	NR	87	NR	NR
Dick, 2007	29	19	NR	NR	NR	NR
Dosluoglu, 2008[b]	27; 27	NR	2; 5	16; 5	29; 2	31; 5
Ah Chong, 2009	79	23	NR	27	NR	31
Dorigo, 2009	38	2	NR	34	NR	68
Korhonen, 2011	51	55	117	NR	NR	14
Bradbury, 2010	53	5	NR	NR	NR	NR

NR, Not reported.
[a]Results are based on the latest reported follow-up period per outcome.
[b]There were two groups of angioplasty interventions (group 1; group 2).

Table V. Summary results of meta-analysis

Outcomes	*OR*	*95% CI*	I^2	*Heterogeneity (P)*	*Interaction (P)*
Mortality	0.72	0.44-1.16	83.4	<.000	—
Hemodynamic criteria[a]	1.13	0.43-2.92	81.8	<.019	.34
Mixed criteria[a]	0.59	0.33-1.06	84.8	<.000	
Single center	0.52	0.31-0.88	75.4	.003	**.001**
Multiple center	1.40	0.93-2.09	35.2	.214	
Cohort	0.52	0.31-0.88	75.4	.003	**.003**
RCTs	1.40	0.93-2.09	35.2	.214	
Amputation (analysis per patient)	1.2	0.87-1.65	51.3	.068	—
Hemodynamic criteria	1.37	0.07-2.67	60.5	.145	.839
Mixed criteria	1.06	0.85-1.31	39.1	.007	
Single center	0.92	0.73-1.16	0	.64	**.005**
Multiple center	2.02	1.23-3.33	0.0	.989	
Cohort	0.92	0.73-1.16	0.0	.64	**.005**
RCTs	2.02	1.23-3.33	0.0	.989	
Limb loss (analysis per limb)	0.69	0.46-1.01	—	—	—
Primary patency	2.5	1.25-4.99	64.8	.036	
Hemodynamic criteria	2.44	1.88-3.17	16.9	.292	.12
Mixed criteria	1.45	0.78-2.70	—	—	
Single center	2.44	1.88-3.17	16.9	.292	.12
Multiple center	1.45	0.78-2.70	—	—	
Cohort	3.15	1.41-7.03	58	.093	.13
RCTs	1.45	0.78-2.70	—	—	
Secondary patency	1.61	0.43-6.01	89.3	<.000	
Assisted primary patency	3.39	1.53-7.51	—	—	

CI, Confidence interval; *OR*, odds ratio; *RCTs*, randomized clinical trials.
Boldface entries indicate statistical significance.
[a]Type of diagnostic criteria used to ascertain the diagnosis of critical limb ischemia (CLI).

Table VI. Summary results of meta-analysis of included studies stratified by outcome and duration of follow-up period

Follow-up duration	*OR*	*95% CI*	I^2	*Heterogeneity (P)*
Mortality				
First year	0.68	0.49-0.93	24.8	.263
Second year	0.65	0.47-0.88	—	—
Third year	0.78	0.62-0.98	0.0	.858
Fourth year	1.12	0.47-2.71	87.6	.036
Fifth year	0.62	0.30-1.29	91	<.000
Actual limb loss				
First year	0.55	0.34-0.89	—	—
Second year	0.69	0.46-1.01	0.0	.812
Third year	0.62	0.42-0.91	—	—
Fourth year	0.56	0.39-0.82	—	—
Fifth year	0.49	0.34-0.71	—	—
Limb loss per patient				
First year	1.2	0.6-2.41	72.5	.012
Second year	0.8	0.6-1.07	—	—
Third year	1.4	0.61-3.23	81.3	.021
Fourth year	1.34	0.73-2.47	58.2	.091
Fifth year	1.1	0.74-1.63	49.5	.138
Primary patency				
First year	1.81	1.29-2.53	0.0	.829
Second year	3.62	1.72-7.65	—	—
Third year	3.07	1.87-5.05	30.9	.235
Fourth year	1.45	0.78-2.70	—	—
Fifth year	3.62	1.52-8.64	—	—
Assisted primary patency				
First year	1.4	0.65-3.01	—	—
Second year	2.38	1.16-4.91	—	—
Third year	3.39	1.53-7.51	—	—
Secondary patency				
First year	1.01	0.36-2.84	89.2	<.000
Second year	0.85	0.12-6.17	94.8	<.000
Third year	1.58	0.33-7.45	95.4	<.000
Fourth year	0.58	0.37-0.90	—	—
Fifth year	0.58	0.37-0.90	—	—

CI, Confidence interval; *OR*, odds ratio.

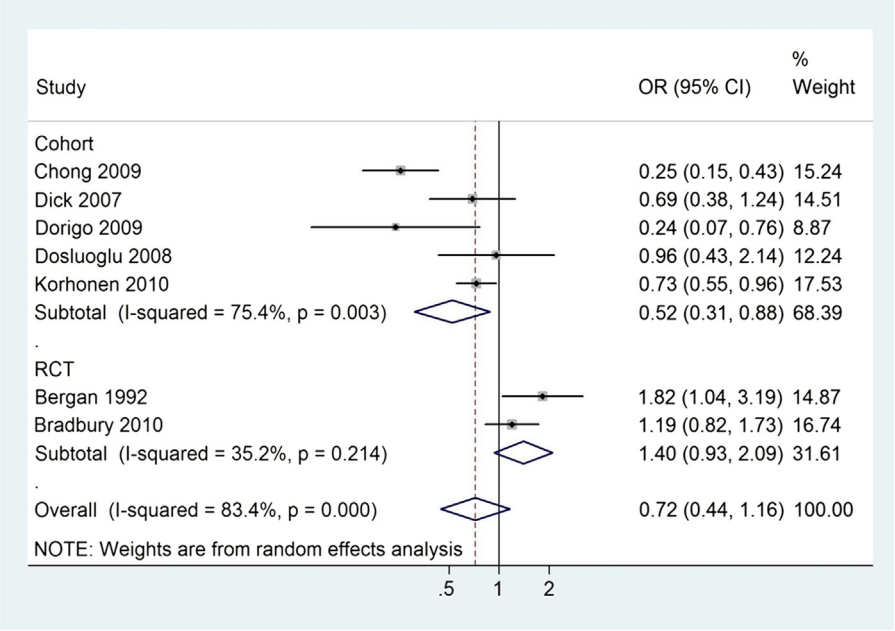


Fig 2. Mortality in patients receiving bypass surgery vs endovascular treatment based on study design. *CI,* Confidence interval; *OR,* odds ratio; *RCT,* randomized clinical trial.

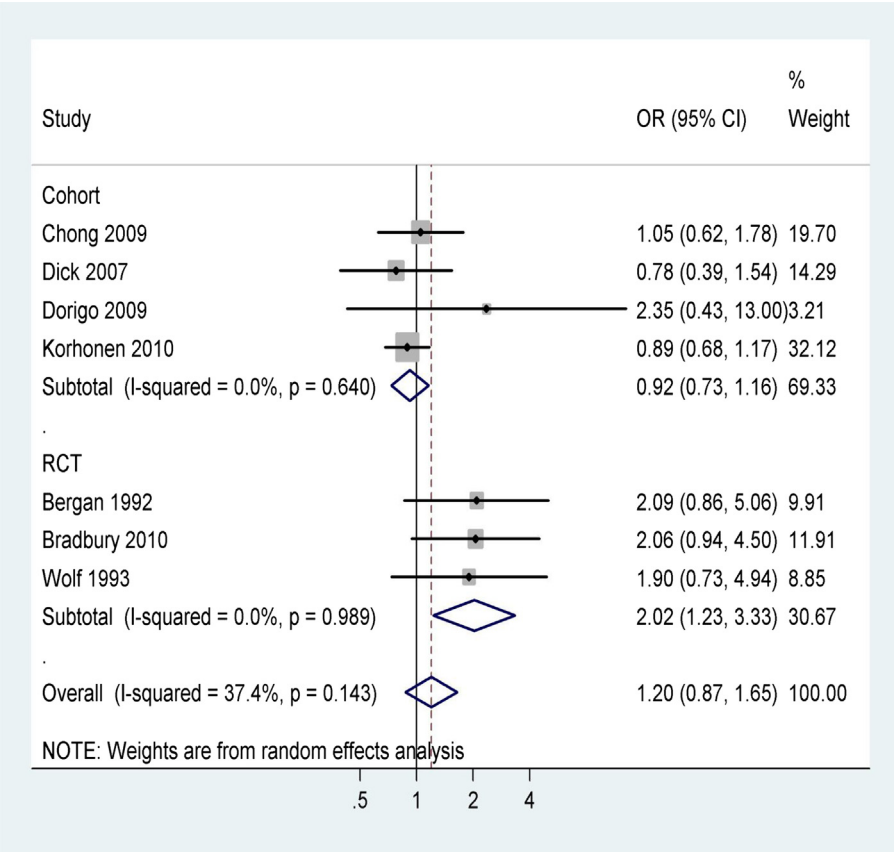


Fig 3. Limb loss (by number of patients) in patients receiving bypass surgery vs endovascular treatment based on study design. *CI,* Confidence interval; *OR,* odds ratio; *RCT,* randomized clinical trial.

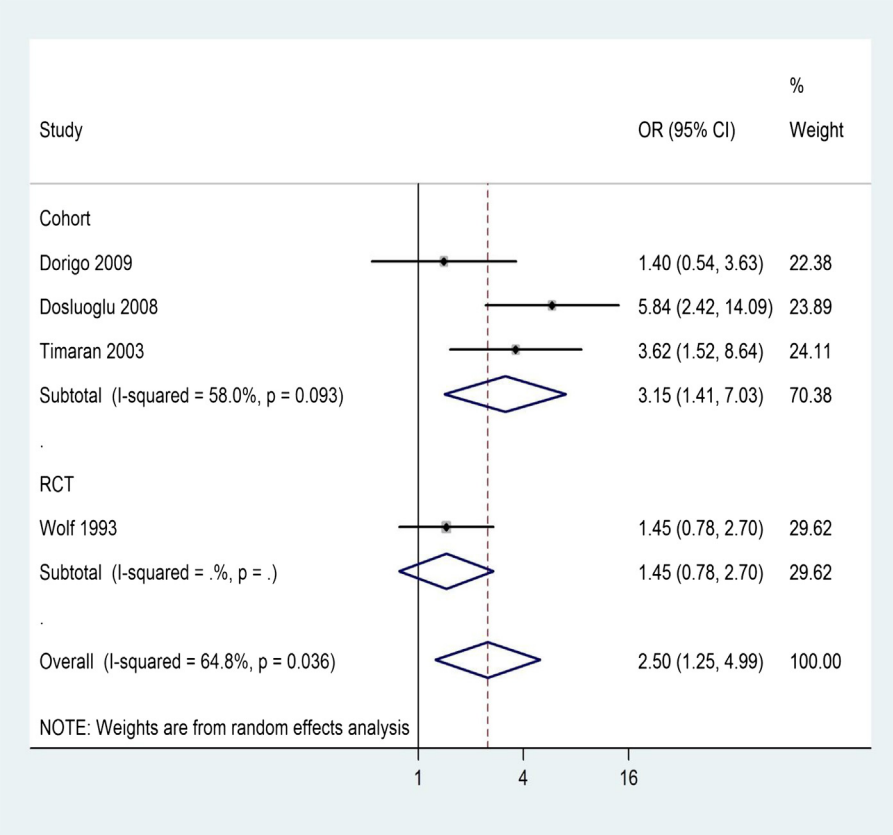


Fig 4. Primary patency in patients receiving bypass surgery vs endovascular treatment. *CI,* Confidence interval; *OR,* odds ratio; *RCT,* randomized clinical trial.

in secondary patency. The OR reported for the assisted primary patency is from one study. Subgroup analyses of patency outcomes did not reveal any significant interactions. All these outcomes were as shown in Supplementary Figs 1-8 (online only).

There were insufficient data to assess the effect on wound healing. Attempts to stratify end points using the SVS Lower Extremity Threatened Limb Classification System[12] were not possible because of insufficient reporting of variables of interest.

The quality of evidence (confidence in the estimate) varied by outcome: low for mortality (due to imprecision and heterogeneity); low for limb loss (imprecise estimates when data analyzed per patient with CI combining appreciable benefits and harms); and moderate for patency (mainly due to heterogeneity).

DISCUSSION

We conducted a systematic review and meta-analysis examining the effect of bypass surgery and endovascular intervention in patients with CLI. Bypass surgery and endovascular approaches did not have significant differences on mortality and major amputations. We found that better primary and primary assisted patency are more likely with bypass. However, quality of evidence was limited by variable definitions, nonstandardized end-point reporting, limited observation times, and heterogeneity in the cohorts.

Outcomes relevant to patients with CLI also include repeated interventions, recurrent pain or symptoms, and quality of life. The SVS document on suggested objective performance goals[14] defined a major adverse limb event (MALE) as a key outcome measure for comparison of revascularization strategies. MALE includes major amputation as well as major target limb reintervention (new open bypass graft, thrombectomy/thrombolysis, or major surgical revision of an existing bypass). Unfortunately, available studies lack reporting of these important end points, which provide a broader picture of the impact of a selected intervention.

The TASC II recommends revascularization as the optimal treatment for patients with CLI[1]; however, the choice of procedure remains unclear. The American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines concluded that in patients with CLI and a life expectancy of >2 years, bypass

surgery is a reasonable initial treatment. For those who do not have an autogenous vein conduit available, balloon angioplasty is a reasonable initial choice.[4]

Until more robust data providing estimates in which we have higher confidence, the choice of revascularization strategy depends on the surgeon's expertise as well as on the patients' values and preferences, expected perioperative risk, and anticipated long-term survival. Given the broad heterogeneity of this clinical syndrome, future studies should appropriately stratify patients (eg, SVS Lower Extremity Threatened Limb Classification System) to improve the fidelity of outcomes reporting and the conduct of comparative effectiveness studies in this field.

There are several limitations to this review. Inference is limited by heterogeneity between the studies (in terms of inclusion criteria, anatomic and severity differences of occluded vessels) and imprecision (small number of small studies). Prior systematic reviews that evaluated lower extremity revascularization highlighted similar uncertainties.[22,23] The strengths of this systematic review include our exhaustive search, rigorous methodology, and adherence to the TASC II definition of CLI.

CONCLUSIONS

Low quality of evidence due to imprecision and heterogeneity suggests that bypass surgery and endovascular approaches may have similar effect on mortality and major amputations. However, better primary and primary assisted patency can be expected with surgery. Future studies should employ additional relevant end points (eg, MALE and reintervention-free survival) and stratification such as the SVS Lower Extremity Threatened Limb Classification System to allow meaningful comparison of treatment modalities across the broad spectrum of patients with advanced limb ischemia.

The authors would like to thank Mr Larry J. Prokop from Mayo Library System, Mayo Clinic, Rochester, Minn, for his significant contribution to our work.

AUTHOR CONTRIBUTIONS

Conception and design: MC, MM
Analysis and interpretation: AAD, MS, MC, MM
Data collection: AAD, MS, NA, CU, ZW, ME
Writing the article: AAD, MS, NA, CU, 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, ZW
Obtained funding: AAD, MS, MM
Overall responsibility: MM
AAD and MS contributed equally to this article and share co-first authorship.

REFERENCES

1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg 2007;33(Suppl 1):S1-75.
2. Tendera M, Aboyans V, Bartelink ML, Baumgartner I, Clement D, Collet JP, et al. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). Eur Heart J 2011;32:2851-906.
3. Arain SA, White CJ. Endovascular therapy for critical limb ischemia. Vasc Med 2008;13:267-79.
4. Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss LK, et al. 2011 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Peripheral Artery Disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011;58:2020-45.
5. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: an intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. J Vasc Surg 2010; 51(Suppl):5S-17S.
6. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009;62:e1-34.
7. Murad MH, Swiglo BA, Sidawy AN, Ascher E, Montori VM. Methodology for clinical practice guidelines for the management of arteriovenous access. J Vasc Surg 2008;48(Suppl):26S-30S.
8. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed March 21, 2015.
9. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions version 5.0.2 [updated September 2009]. London, UK: The Cochrane Collaboration; 2009.
10. Diehm N, Baumgartner I, Jaff M, Do DD, Minar E, Schmidli J, et al. A call for uniform reporting standards in studies assessing endovascular treatment for chronic ischaemia of lower limb arteries. Eur Heart J 2007;28:798-805.
11. Dosluoglu HH, Cherr GS, Lall P, Harris LM, Dryjski ML. Stenting vs above knee polytetrafluoroethylene bypass for TransAtlantic Inter-Society Consensus-II C and D superficial femoral artery disease. J Vasc Surg 2008;48:1166-74.
12. Mills JL Sr, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIfI). J Vasc Surg 2014;59: 220-34.e1-2.
13. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
14. Conte MS, Geraghty PJ, Bradbury AW, Hevelone ND, Lipsitz SR, Moneta GL, et al. Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. J Vasc Surg 2009;50:1462-73.e1-3.
15. Bergan JJ, Wilson SE, Wolf G, Deupree RH. Unexpected, late cardiovascular effects of surgery for peripheral artery disease. Veterans Affairs Cooperative Study 199. Arch Surg 1992;127:1119-23; discussion: 1123-4.
16. Wolf GL, Wilson SE, Cross AP, Deupree RH, Stason WB. Surgery or balloon angioplasty for peripheral vascular disease: a randomized clinical trial. Principal investigators and their Associates of Veterans Administration Cooperative Study Number 199. J Vasc Interv Radiol 1993;4:639-48.

17. Ah Chong AK, Tan CB, Wong MW, Cheng FS. Bypass surgery or percutaneous transluminal angioplasty to treat critical lower limb ischaemia due to infrainguinal arterial occlusive disease? Hong Kong Med J 2009;15:249-54.
18. Dick F, Diehm N, Galimanis A, Husmann M, Schmidli J, Baumgartner I. Surgical or endovascular revascularization in patients with critical limb ischemia: influence of diabetes mellitus on clinical outcome. J Vasc Surg 2007;45:751-61.
19. Dorigo W, Pulli R, Marek J, Troisi N, Fargion A, Giacomelli E, et al. A comparison between open and endovascular repair in the treatment of critical limb ischemia. Ital J Vasc Endovasc Surg 2009;16:17-22.
20. Korhonen M, Biancari F, Soderstrom M, Arvela E, Halmesmaki K, Alback A, et al. Femoropopliteal balloon angioplasty vs. bypass surgery for CLI: a propensity score analysis. Eur J Vasc Endovasc Surg 2011;41:378-84.
21. Timaran CH, Prault TL, Stevens SL, Freeman MB, Goldman MH. Iliac artery stenting versus surgical reconstruction for TASC (Trans-Atlantic Inter-Society Consensus) type B and type C iliac lesions. J Vasc Surg 2003;38:272-8.
22. Fowkes F, Leng GC. Bypass surgery for chronic lower limb ischaemia. Cochrane Database Syst Rev 2008;2:CD002000.
23. Muradin GS, Bosch JL, Stijnen T, Hunink MG. Balloon dilation and stent implantation for treatment of femoropopliteal arterial disease: meta-analysis. Radiology 2001;221:137-45.

Submitted Mar 15, 2015; accepted Jul 10, 2015.

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 46, 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 2014

#	*Searches*	*Results*
1	exp Ischemia/	455614
2	exp peripheral occlusive artery disease/	87563
3	exp Peripheral Vascular Diseases/	950368
4	exp Atherosclerosis/	143727
5	exp arteriosclerosis/	272300
6	exp intermittent claudication/	13290
7	exp Arterial Occlusive Diseases/	264275
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]	1164954
9	or/1-8	1688483
10	exp Leg/	156979
11	exp Leg Ulcer/	24967
12	exp lower extremity/	227598
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]	970598
14	or/10-13	977126
15	9 and 14	110088
16	exp Ablation Techniques/	90673
17	exp ablation therapy/	3941
18	exp radiofrequency ablation/	12657
19	exp laser surgery/	92005
20	exp catheter ablation/	38647
21	exp cyanoacrylate/	5283
22	exp sclerotherapy/	13193
23	exp endovascular surgery/	14778
24	exp angioplasty/	116997
25	exp stent/	135796
26	exp Endovascular Procedures/	94396
27	(((endovenous or endovascular or ablation or ablative or "radio frequency" or radiofrequency or laser* or steam or clarivein or Cyanoacrylate or glue or sclerotherap* or sclerosation or sclerozation or sclerosing) adj2 (therap* or care or treatment* or surg* or procedure*)) or angioplast* or "endoluminal repair*" or stent* or atherectom*).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui, tx, ct]	400912
28	or/16-27	516107
29	exp leg revascularization/	3986
30	blood vessel shunt/	2260
31	bypass surgery/	52065
32	exp shunting/	4966
33	(bypass* or graft* or "anastomosis vascularis" or "vessel anastomosis" or "vascular anastomosis" or shunt* or revascular iz*).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui, tx, ct]	971063
34	or/29-33	971078
35	15 and 28 and 34	5602
36	exp Survival Analysis/ or exp Survival/ or exp Survival Rate/	759187
37	exp Wound Healing/	167811
38	exp amputation/	38966
39	(survival or (heal* adj3 (wound* or injur*)) or (limb* adj3 (loss or lose or losing)) or amputat* or patency).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui, tx, ct]	1824236
40	exp vascular patency/ or exp graft patency/	23935

(*Continued on next page*)

Continued.

#	*Searches*	*Results*
41	or/36-40	1899315
42	35 and 41	3475
43	exp controlled study/	3976677
44	exp evidence based medicine/	609305
45	evidence-based.mp.	205847
46	((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]	5094743
47	meta analysis/	104932
48	meta-analys$.mp.	168969
49	exp "systematic review"/	54671
50	(systematic* adj review$).mp.	128469
51	exp Guideline/ or exp Practice Guideline/	303843
52	guideline$.ti.	97229
53	or/43-52	5692874
54	42 and 53	800
55	from 42 keep 1895-3370	1476
56	limit 55 to (controlled clinical trial or guideline or practice guideline or randomized controlled trial) [Limit not valid in Embase,CDSR; records were retained]	77
57	54 or 56	800
58	limit 57 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]	55
59	57 not 58	745
60	from 42 keep 3371-3475	105
61	59 or 60	821
62	remove duplicates from 61	641

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(bypass* or graft* or "anastomosis vascularis" or "vessel anastomosis" or "vascular anastomosis" or shunt* or revascular iz*)

4 TITLE-ABS-KEY((sclerosing w/2 therap*) or (sclerosing w/2 care) or (sclerosing w/2 treatment*) or (sclerosing w/2 surg*) or (sclerosing w/2 procedure*) or (endovenous w/2 therap*) or (endovenous w/2 care) or (endovenous w/2 treatment*) or (endovenous w/2 surg*) or (endovenous w/2 procedure*) or (endovascular w/2 therap*) or (endovascular w/2 care) or (endovascular w/2 treatment*) or (endovascular w/2 surg*) or (endovascular w/2 procedure*) or (ablation w/2 therap*) or (ablation w/2 care) or (ablation w/2 treatment*) or (ablation w/2 surg*) or (ablation w/2 procedure*) or (ablative w/2 therap*) or (ablative w/2 care) or (ablative w/2 treatment*) or (ablative w/2 surg*) or (ablative w/2 procedure*) or ("radio frequency" w/2 therap*) or ("radio frequency" w/2 care) or ("radio frequency" w/2 treatment*) or

("radio frequency" w/2 surg*) or ("radio frequency" w/2 procedure*) or (radiofrequency w/2 therap*) or (radiofrequency w/2 care) or (radiofrequency w/2 treatment*) or (radiofrequency w/2 surg*) or (radiofrequency w/2 procedure*) or (laser* w/2 therap*) or (laser* w/2 care) or (laser* w/2 treatment*) or (laser* w/2 surg*) or (laser* w/2 procedure*) or (steam w/2 therap*) or (steam w/2 care) or (steam w/2 treatment*) or (steam w/2 procedure*) or (clarivein w/2 therap*) or (clarivein w/2 care) or (clarivein w/2 treatment*) or (clarivein w/2 surg*) or (clarivein w/2 procedure*) or (Cyanoacrylate w/2 therap*) or (Cyanoacrylate w/2 care) or (Cyanoacrylate w/2 treatment*) or (Cyanoacrylate w/2 surg*) or (Cyanoacrylate w/2 procedure*) or (glue w/2 therap*) or (glue w/2 care) or (glue w/2 treatment*) or (glue w/2 procedure*) or sclerotherap* or (sclerosation w/2 therap*) or (sclerosation w/2 care) or (sclerosation w/2 treatment*) or (sclerosation w/2 surg*) or (sclerosation w/2 procedure*) or (sclerozation w/2 therap*) or (sclerozation w/2 care) or (sclerozation w/2 treatment*) or (sclerozation w/2 surg*) or (sclerozation w/2 procedure*))

5 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* or patency)

6 TITLE-ABS-KEY((meta W/1 analys*) OR (systematic* W/2 review*) OR (control* W/2 stud*) OR (control* W/2 trial*) OR (randomized W/2 stud*) OR (randomized W/2 trial*))

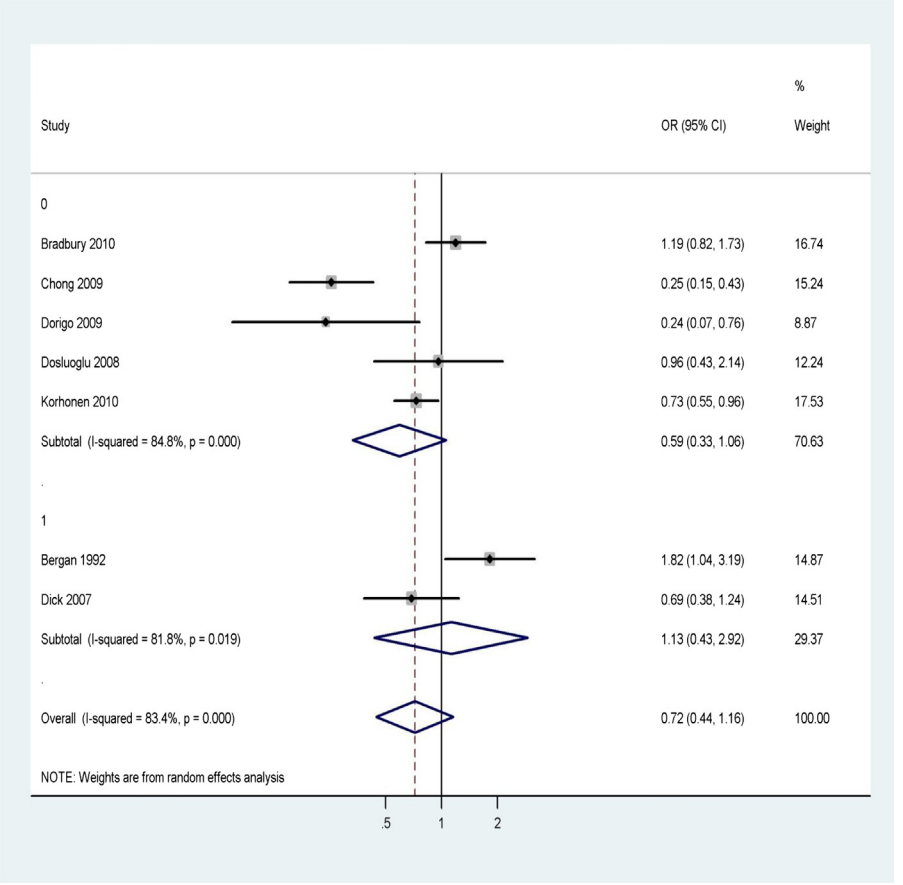
7 1 and 2 and 3 and 4 and 5 and 6

8 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*)

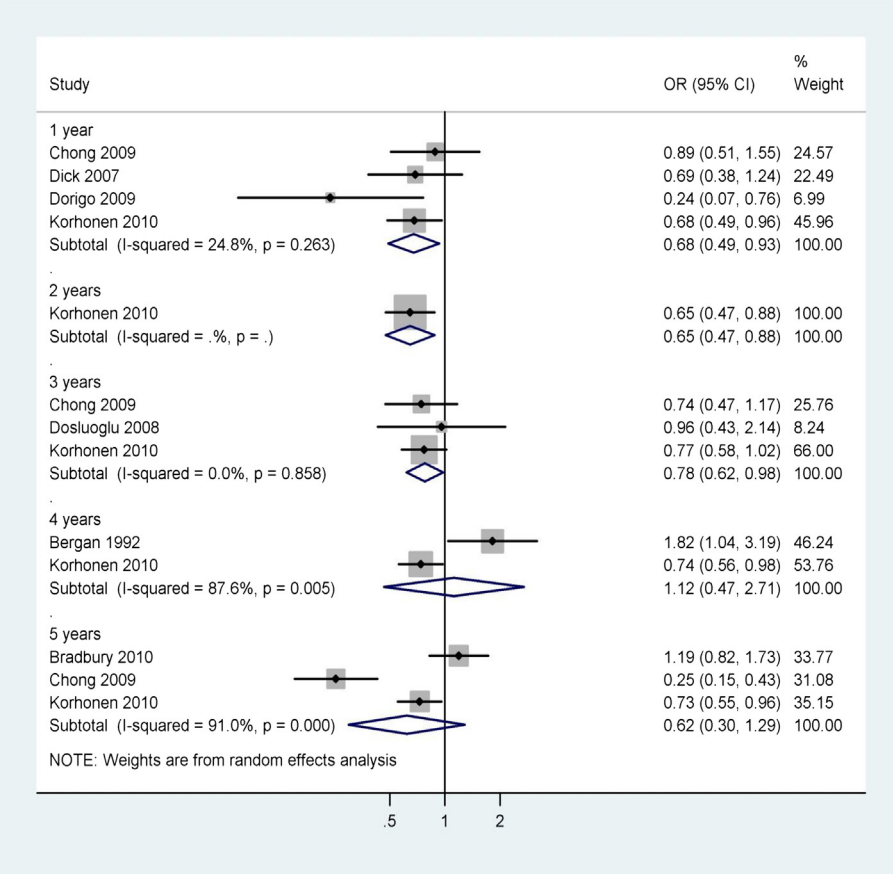
9 7 and not 8

10 DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)

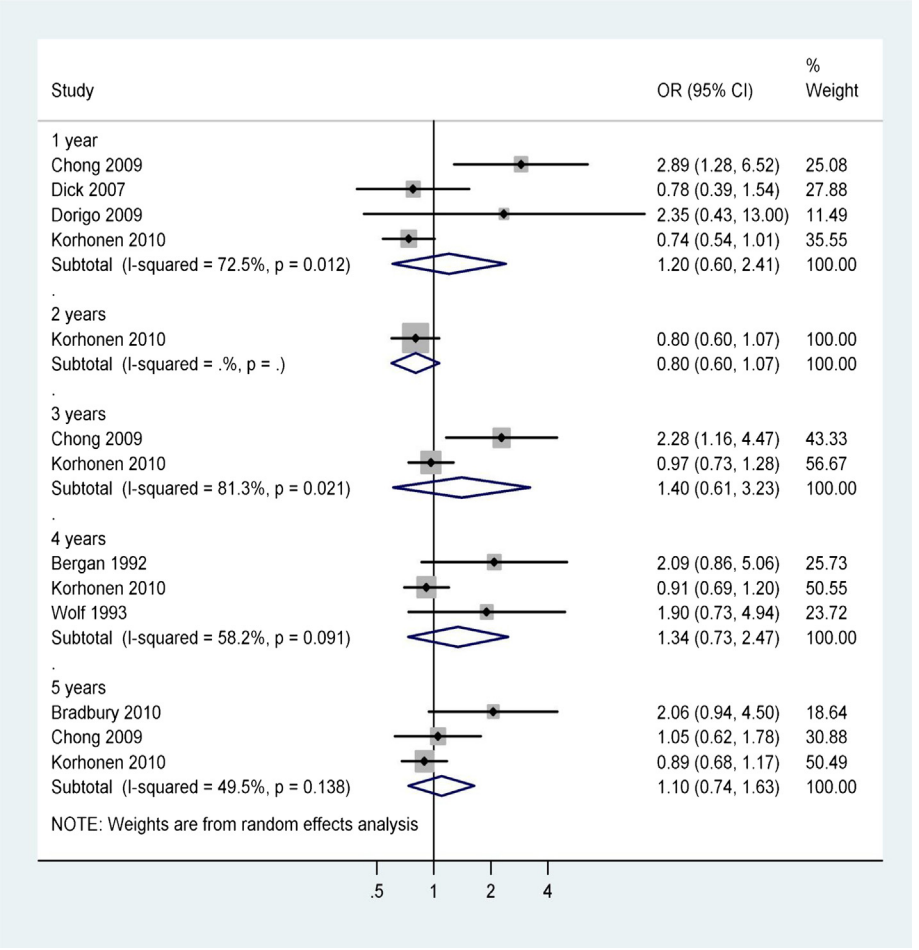
11 9 and not 10



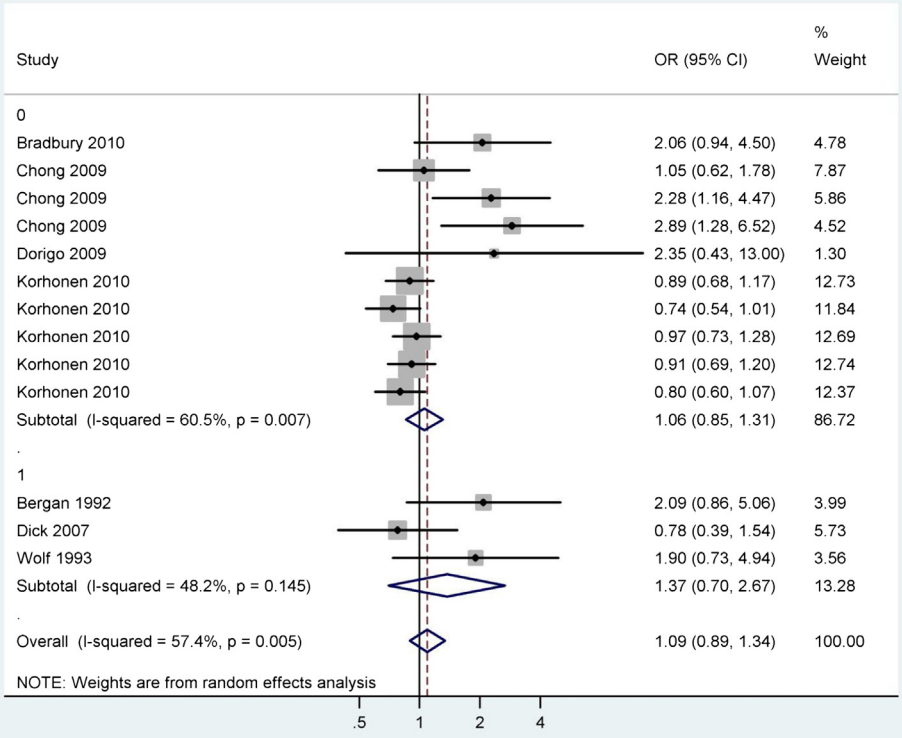
Supplementary Fig 1 (online only). Mortality in patients who received bypass surgery vs endovascular treatment based on use of diagnostic criteria [mixed (0) vs hemodynamic (1)]. *CI*, Confidence interval; *OR*, odds ratio.



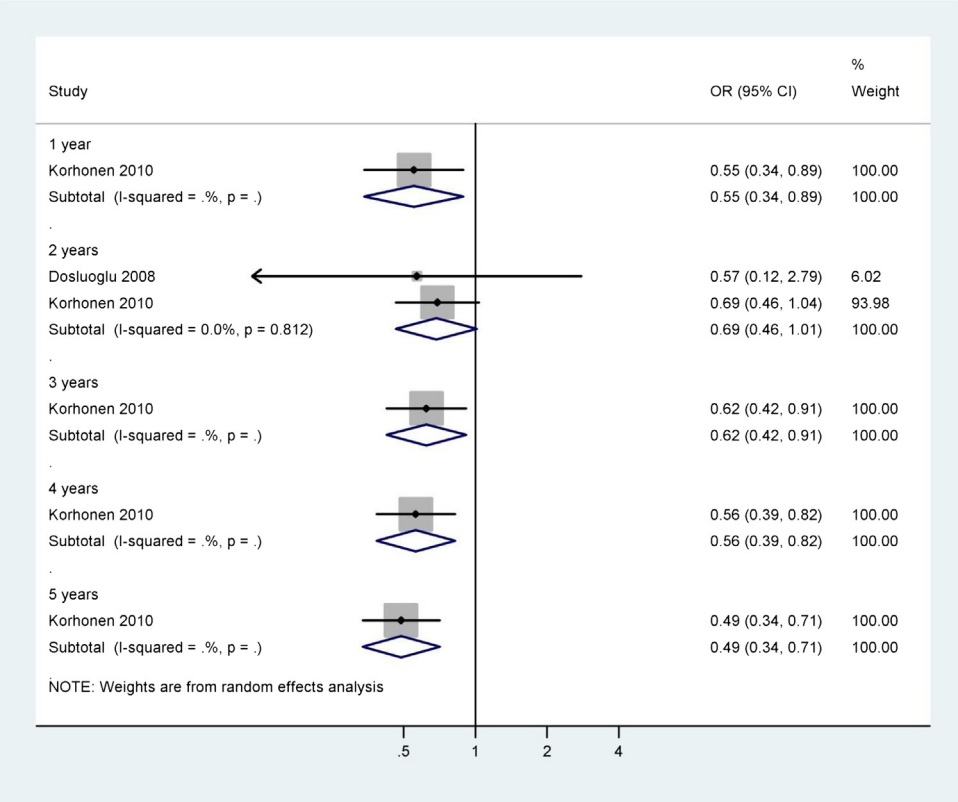
Supplementary Fig 2 (online only). Mortality in patients who received bypass surgery vs endovascular treatment by year of follow-up. *CI*, Confidence interval; *OR*, odds ratio.



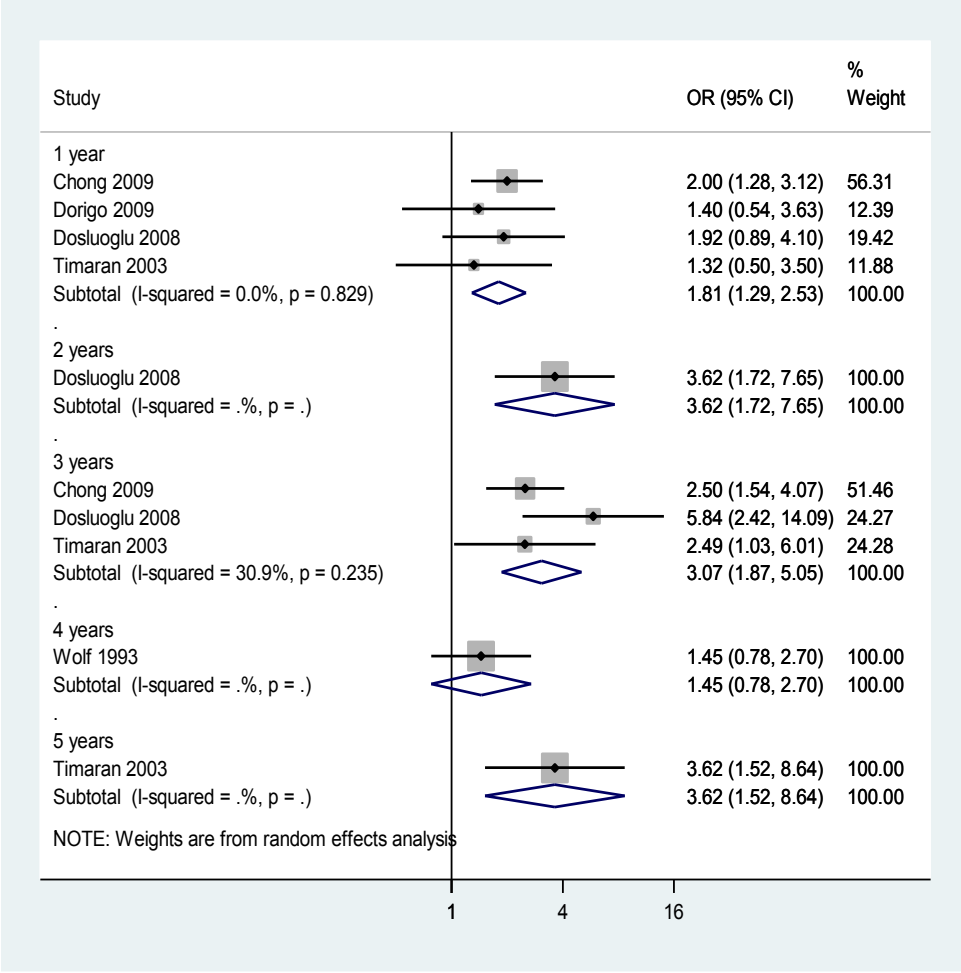
Supplementary Fig 3 (online only). Limb loss (by number of patients) in patients who received bypass surgery vs endovascular treatment based on follow-up year. *CI*, Confidence interval; *OR*, odds ratio.



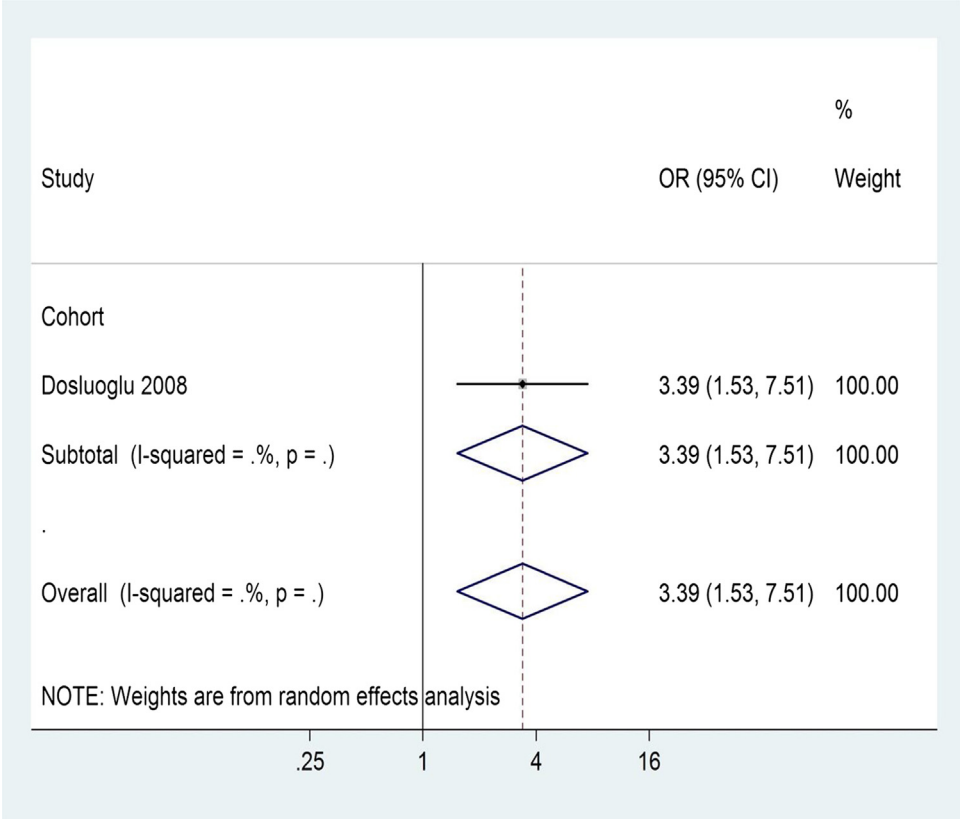
Supplementary Fig 4 (online only). Limb loss (by number of patients) in patients who received bypass surgery vs endovascular treatment based on use of criteria [mixed (0) vs hemodynamic (1)]. *CI*, Confidence interval; *OR*, odds ratio.



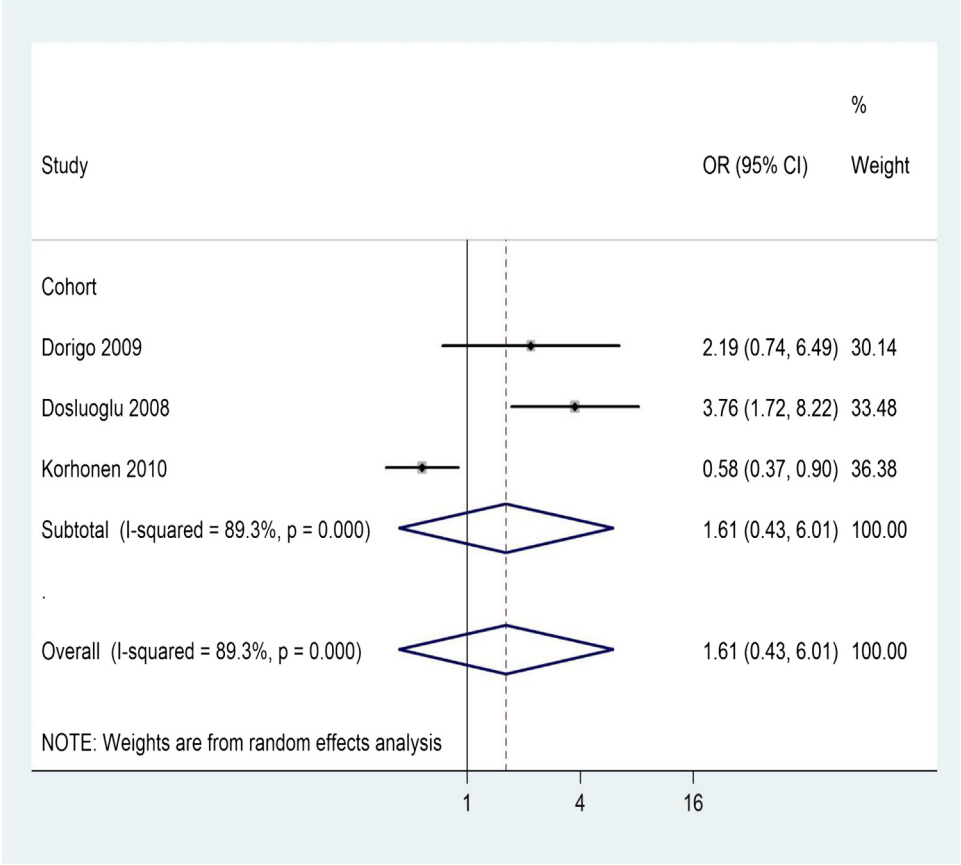
Supplementary Fig 5 (online only). Limb loss (by number of limbs) in patients who received bypass surgery vs endovascular treatment. *CI,* Confidence interval; *OR,* odds ratio.



Supplementary Fig 6 (online only). Primary patency in patients who received bypass surgery vs endovascular treatment by year of follow-up. *CI*, Confidence interval; *OR*, odds ratio.



Supplementary Fig 7 (online only). Assisted primary patency in patients who received bypass surgery vs endovascular treatment. *CI,* Confidence interval; *OR,* odds ratio.



Supplementary Fig 8 (online only). Secondary patency in patients who received bypass surgery vs endovascular treatment. *CI,* Confidence interval; *OR,* odds ratio.