APPENDIX A. SEARCH STRATEGY

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 1/1/2018-1/16/2019

LANGUAGE:
English

SEARCH STRATEGY:
peripheral arterial disease[mh] OR critical limb ischemia[mh] OR intermittent claudication[mh] OR critical limb ischemia[tiab] OR critical limb ischemia[ot] OR peripheral artery disease* OR peripheral arterial disease* OR peripheral vascular disease* OR claudication OR limb ischemia or limb threat* OR (ischaemia AND (leg OR legs OR limb OR limbs))

AND

vascular graft* OR amputat* OR blood vessel prosthesis implantation OR endovascular procedure* OR vascular surgical procedure* OR limb salvage OR endovascular OR bypass OR angioplast* OR stent OR stents OR atherectom* OR saphenous vein* OR drug coated balloon*

AND

vascular surgical procedures[MH] OR surgery[tiab] OR surgery[ot] OR surgical[tiab] OR surgical[ot]

AND

"Costs and Cost Analysis"[Mesh] OR "Economics"[Mesh] OR "economics" [Subheading] OR "Cost Savings"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR "Hospital Costs"[Mesh] OR "Health Expenditures"[Mesh] OR "utilization" [Subheading] OR "Length of Stay"[Mesh] OR "Patient Readmission"[Mesh] OR "Reoperation"[Mesh] OR expensive[tiab] OR cost-effective*[tiab] OR costs[tiab] OR cost[tiab] OR cost-consequence*[tiab] OR cost effective*[tiab] OR economic*[tiab] OR economic-based[tiab] OR cost-saving*[tiab] OR utilization OR "length of stay" OR readmission* OR readmit* OR reoperation* OR re-operation OR "procedure time"

DATABASE SEARCHED & TIME PERIOD COVERED:
Embase – 1/1/2018-1/17/2019

LANGUAGE:
English

OTHER LIMITERS:
Human

SEARCH STRATEGY:
('critical limb ischemia'/exp OR 'critical limb ischemia' OR 'peripheral occlusive artery disease'/exp OR 'peripheral occlusive artery disease' OR 'intermittent claudication'/exp OR 'intermittent claudication' OR (limb NEAR/2 ischemia) OR ((peripheral NEAR/2 artery NEAR/2 disease*):ti,ab,kw) OR ((peripheral NEAR/2 arterial NEAR/2 disease*):ti,ab,kw) OR ((peripheral NEAR/2 vascular NEAR/2 disease*):ti,ab,kw) OR 'claudication'/exp OR 'claudication' OR claudication:ti,ab,kw OR ((limb NEAR/2

threat*):ti,ab,kw) OR ((ischaemia:ti,ab,kw OR ischemi*:ti,ab,kw) AND (leg:ti,ab,kw OR legs:ti,ab,kw OR limb:ti,ab,kw OR limbs:ti,ab,kw)))

AND

((vascular NEAR/2 graft*) OR amputat* OR (blood NEAR/2 vessel NEAR/2 prosthesis NEAR/2 implant*) OR (endovascular NEAR/2 procedure*) OR (limb NEAR/2 salvag*) OR endovascular OR bypass OR angioplast* OR stent OR stents OR atherectom* OR (saphenous NEAR/2 vein*) OR (drug NEAR/2 coated NEAR/2 balloon*))

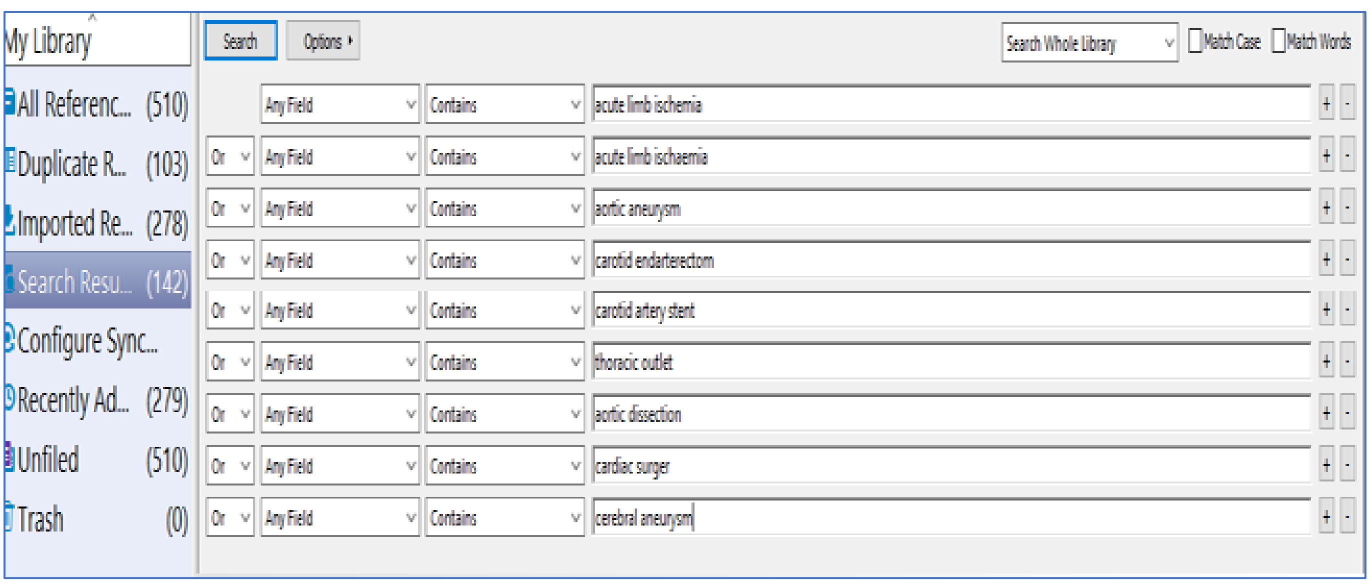
AND

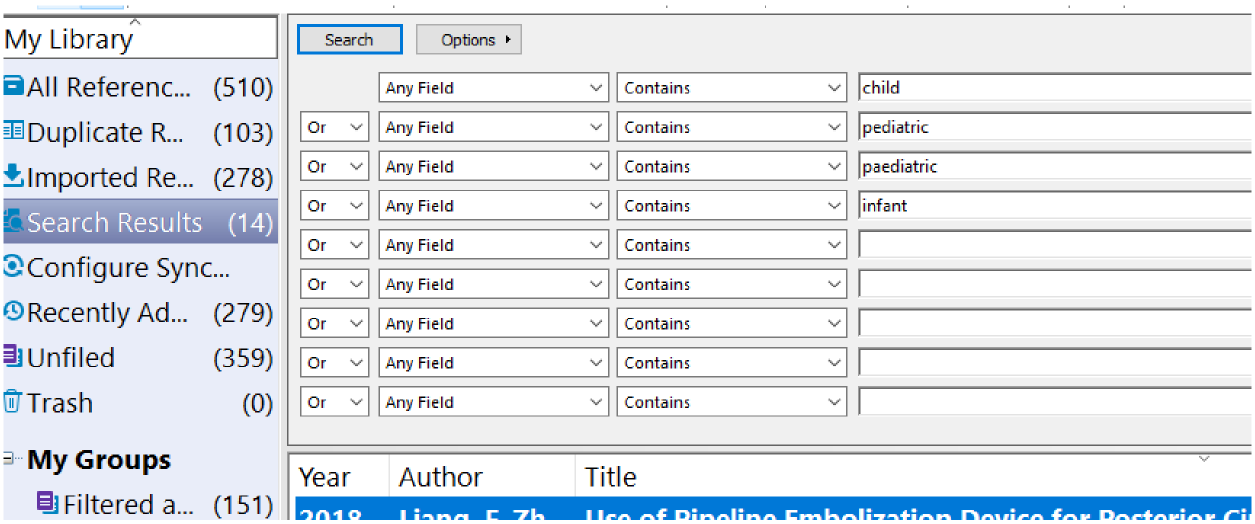
('vascular surgery'/exp OR surgery:ti,ab,kw OR surgical:ti,ab,kw OR (vascular NEAR/2 surgical) OR (vascular NEAR/2 surgery))

AND

('cost'/exp OR 'economics'/exp OR 'hospital cost'/exp OR 'health care cost'/exp OR 'utilization'/exp OR 'length of stay'/exp OR 'hospital readmission'/exp OR 'reoperation'/exp OR 'cost control'/exp OR 'cost benefit analysis'/exp OR economic* OR utilization OR 'length of stay' OR readmission* OR readmit* OR reoperat* OR 're-operation' OR (procedure NEAR/2 time) OR cost:ti,ab,kw OR costs:ti,ab,kw)

NOTE: ALL RESULTS WERE SEARCHED IN ENDNOTE WITH THE FOLLOWING TERMS TO IDENTIFY POTENTIALLY NON-RELEVANT ARTICLES. RECORDS IDENTIFIED WERE TAGGED AS FILTERED FOR NON-RELEVANCE:




My Library
All Referenc... (510)
Duplicate R... (103)
Imported Re... (278)
Search Results (14)
Configure Sync...
Recently Ad... (279)
Unfiled (359)
Trash (0)
My Groups
Filtered a... (151)
Search
Options
Any Field Contains child
Or Any Field Contains pediatric
Or Any Field Contains paediatric
Or Any Field Contains infant
Or Any Field Contains
Or Any Field Contains
Or Any Field Contains
Or Any Field Contains
Or Any Field Contains
Year
Author
Title

APPENDIX B. PEER REVIEWER COMMENTS AND RESPONSES

Comment	Response
The comparison to CAD is quite germane and should be expanded a bit further to emphasize the underlying foundational gaps in definitions, disease staging, and endpoints that have plagued evidence based medicine in PAD in general. In CAD, disease staging (both anatomic and functional) is well established and has allowed clinical research including RCTs to provide guidelines relevant to both practitioners and the referring community. The clinical and anatomic spectrum of "CLI" is extremely broad, arguably broader than that of CAD -- particularly given the multi-level patterns of arterial occlusive disease as well as the spectrum of limb threat encountered. Accordingly improved disease staging, such as that suggested in the Society for Vascular Surgery Threatened Limb Classification System, will be critical to develop comparative evidence in this field. The optimal approach for ischemic rest pain, minor ulcers without infection, and major tissue loss with infection are likely to be different.	These are great comments and we have made changes to the discussion in response
Similarly, the lack of an integrated anatomic staging system for the limb focused on patterns of disease rather than the lesion-focused lexicon of PAD is another major gap. Effective revascularization in CLI generally requires restoring in-line flow to the ankle and foot; multi-level occlusive disease is the rule rather than the exception. As anatomic pattern of disease is currently a (or possibly the) primary factor driving selection of open versus endovascular treatment, relevant comparisons cannot be made without considering this key element. If one considers the parallel to CAD, any comparison of PCI versus CABG that did not clarify the anatomic context would be considered irrelevant. This critical issue was not addressed in the Discussion.	
Endpoints in PAD/CLI, both clinical and patient-focused, have also lacked consensus. Few would argue with the pre-eminence of mortality and major amputation. However, freedom from recurrent symptoms of CLI and re-interventions are also of great importance to patients. A composite endpoint of freedom from reintervention, recurrent CLI, amputation or death might be the most clinically meaningful. Moreover, from the standpoint of both clinical effectiveness and cost-effectiveness a time-integrated measure would be of greater relevance in a chronic disease like CLI rather than a time-to-first event approach. Please comment on this concept, which may be important for future research in this arena.	
There is inconsistent definition of KQ 2 re limited to CLI or including claudication in different parts of the manuscript	This was edited
You may want to consider the following information and add it to your write-up https://www.ahajournals.org/doi/10.1161/ JAHA.118.011245	This study compared 2 types of endovascular therapy, and there is no surgical therapy comparison, hence it did not meet inclusion criteria. Nevertheless, it is a possible signal of concern about one type of stent.

APPENDIX C. COCHRANE RISK OF BIAS TOOL

The Cochrane Collaboration's Tool for Assessing Risk of Bias*

Domain	Support for judgement	Review authors' judgement
Selection bias.		
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias.		
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias.		
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition bias.		
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias.		
Selective reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias.		
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

* http://handbook.cochrane.org/ in Table 8.5.a

APPENDIX D. RISK OF BIAS IN NON-RANDOMISED STUDIES – OF INTERVENTIONS (ROBINS-I)

Bias domains included in ROBINS-I[10]

Pre-intervention	Risk of bias assessment is mainly distinct from assessments of randomised trials
Bias due to confounding	Baseline confounding occurs when one or more prognostic variables (factors that predict the outcome of interest) also predicts the intervention received at baseline ROBINS-I can also address time-varying confounding, which occurs when individuals switch between the interventions being compared and when post-baseline prognostic factors affect the intervention received after baseline
Bias in selection of participants into the study	When exclusion of some eligible participants, or the initial follow-up time of some participants, or some outcome events is related to both intervention and outcome, there will be an association between interventions and outcome even if the effects of the interventions are identical This form of selection bias is distinct from confounding—A specific example is bias due to the inclusion of prevalent users, rather than new users, of an intervention
At intervention	Risk of bias assessment is mainly distinct from assessments of randomised trials
Bias in classification of interventions	Bias introduced by either differential or non-differential misclassification of intervention status Non-differential misclassification is unrelated to the outcome and will usually bias the estimated effect of intervention towards the null Differential misclassification occurs when misclassification of intervention status is related to the outcome or the risk of the outcome, and is likely to lead to bias
Post-intervention	Risk of bias assessment has substantial overlap with assessments of randomised trials
Bias due to deviations from intended interventions	Bias that arises when there are systematic differences between experimental intervention and comparator groups in the care provided, which represent a deviation from the intended intervention(s) Assessment of bias in this domain will depend on the type of effect of interest (either the effect of assignment to intervention or the effect of starting and adhering to intervention).
Bias due to missing data	Bias that arises when later follow-up is missing for individuals initially included and followed (such as differential loss to follow-up that is affected by prognostic factors); bias due to exclusion of individuals with missing information about intervention status or other variables such as confounders
Bias in measurement of outcomes	Bias introduced by either differential or non-differential errors in measurement of outcome data. Such bias can arise when outcome assessors are aware of intervention status, if different methods are used to assess outcomes in different intervention groups, or if measurement errors are related to intervention status or effects
Bias in selection of the reported result	Selective reporting of results in a way that depends on the findings and prevents the estimate from being included in a meta-analysis (or other synthesis)

APPENDIX E. QUALITY ASSESSMENT FOR INCLUDED RCT STUDY

Author Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Adam, 2005[2]	™	™	˜	™*	™	™	™

™ = low risk of bias ˜ = risk of bias ½ = unknown
* low risk of bias for primary outcomes (all-cause mortality and amputation-free survival, but high risk of bias for secondary outcomes

APPENDIX F. QUALITY ASSESSMENT FOR INCLUDED OBSERVATIONAL STUDIES

Author Year	Confounding	Selection bias	Bias in measurement classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Bisdas 2015[23] Bisdas 2016[24] Meyer 2016[39]	**Serious:** patients **Low**: time	**Low**	**Low**	**Low**	**Low:** in-hospital **Low**: 1-year outcomes	**Low**: in-hospital outcomes **Low**: 1-year outcomes	**Low**
Bodewes 2018[25]	**Serious:** patients **Low**: time	**Moderate**	**Low**	**Low**	**Low**	**Low**	**Low**
Cejna 2011[31]	**Serious**	**No information**	**Low**	**Low**	**Moderate:** efficacy **Moderate**: cost	**Low**: efficacy outcomes **No info:** cost outcomes	**Moderate**
Darling 2017[26]	**Serious**: patients and time	**Low**	**Low**	**Low**	**Low**: short-term outcomes **Serious**: long-term outcomes	**Moderate**: short-term outcomes **Low**: long-term outcomes	**Low**
Darling 2018a[34]	**Serious**: patients **Low:** time	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Dayama 2019[35]	**Serious**: patients **Low:** time	**Low**	**Low**	**Low**	**Low**: short-term outcomes	**No info**	**Low**
Dosluoglu 2006[27]	**Serious**: patients and time	**Low**	**Low**	**Low**	**Low**: short-term outcomes **Moderate**: long-term outcomes	**Low:** short-term outcomes **Low**: long-term outcomes	**Low**
	Confounding	**Selection bias**	**Bias in measurement classification of interventions**	**Bias due to deviations from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of the reported result**

Dosluoglu 2012[28]	**Serious**: patients and time	**Low**	**Low**	**Serious**	**Low**: short-term outcomes **Serious**: long-term outcomes	**Low**: short-term outcomes **Low**: long-term outcomes	**Low**
Gargiulo 2011[32]	**No info**	**Serious**	**Low**	**Low**	**No info**	**No info**	**Moderate**
Kim 2012[33]	**No info**	**No info**	**Low**	**Low**	**Moderate**: efficacy **Moderate**: cost	**Low:** efficacy **No info**: cost outcomes	**Moderate**
Siracuse 2016[36]	**Serious:** patients **Moderate**: time	**Moderate**	**Low**	**Low**	**Low**: short-term outcomes **Serious**: long-term outcomes	**Low:** short-term outcomes **Moderate:** long-term outcomes	**Low**
Taylor 2009[29]	**Serious:** **p**atients **Low**: time	**Moderate**	**Low**	**Low**	**Low**	**Low**	**Low**
Tsai 2015[30]	**Serious:** patients **Low**: time	**Low**	**Low**	**Low**	**Low:** short-term **Moderate**: long-term	**Low**: short-term **Low**: mortality)	**Low**
Werneck 2009[38]	**Serious:** patients **Low**: time	**Low**	**Low**	**Low**	**Low:** short-term outcomes & cost	**Low:** short-term outcomes **Serious:** cost	**Low**

APPENDIX G. EVIDENCE TABLE

Author Year Population	How was CLI defined?	Surgical intervention N Patient characteristics	Endovascular intervention N Patient characteristics	Short-term Outcomes	Long-term Outcomes	Stratification variables
Bisdas 2015[23] German CRITISCH registry (prospective, multicenter, 27 centers)	Rutherford stage 4-6, lasting > 2 weeks: ABI <= 0.4 or pain at rest, or both, with or without tissue loss	Surgical bypass, not patchplasty N = 284 Median age 73 68% male 42% angina/CAD 6% MI w/in 6 months 30% renal insuf 5% dialysis 48% DM 14% obesity 49% previous vascular interv 11% stroke 31% smokers	Any EV intervention except isolated iliac N = 642 Median age 75 63% male 46% angina/CAD 4% MI w/in 6 months 39% renal insuf 10% dialysis 48% DM 14% obesity 39% previous vascular interv 11% stroke 15% smokers	In-hospital, EV vs bypass; Amputation or death 4% vs 6% (p = 0.172; bivariate) Amputation 3% vs 4% (p = 0.67; bivariate) Death 1% vs 3% (p = 0.003; bivariate) Hemodynamic failure 13% vs 8% (p < 0.001; bivariate) MACCE 4% vs 5% (p = 0.097; bivariate) Reintervention 8% vs 14% (p = 0.015; bivariate) Minor amputation 12% vs 14% (p N/A; bivariate) Median LOS 7 days vs 15 days (p <0.001; bivariate) Periprocedural complications 9% vs 26% (p N/A; bivariate)	NA	NA
Bisdas 2016[24] German CRITISCH registry (prospective, multicenter, 27 centers)	ABI < 0.4, rest pain, nonhealing ulcers/gangrene for >2 weeks, Rutherford 4-6	Bypass surgery, NOT patchplasty N=284 Mean age 73 68% Male Dialysis 5% DM 48% BMI > 30 14% Additional details available: Rutherford	EV interventions, not isolated iliac N=642 Mean age 75 63% Male Dialysis 10% DM 48% BMI > 30 14% Additional details available:	EV vs surgery Median LOS 7 days vs 15 days (p<0.001, bivariate) Discharged home 88% vs 75% (p<0.001, bivariate) In-hospital mortality 1% vs 3% (p=0.085, bivariate) In-hospital major amputation 3% vs 4% (p=0.841, bivar) Median f/u ~ 1 year in both groups	NA	NA

Author Year Population	How was CLI defined?	Surgical intervention N Patient characteristics	Endovascular intervention N Patient characteristics	Short-term Outcomes	Long-term Outcomes	Stratification variables
		distribution, TASC, runoff vessels, and type of interventions	Rutherford distribution, TASC, runoff vessels, and type of interventions	AFS at 1 year: 75% vs 72% (p=0.994, bivariate) Multivariate HR 0.91 (95% CI 0.70-1.19, p=0.492), DID claim non inferior Freedom from amputation at 1 year: 90% vs 85% (p=0.077, bivariate) Multivariate HR 0.86 (95% CI 0.56-1.30, p=0.463) Survival at 1 year: 81% vs 84% (p=0.036, bivariate) Multivariate HR 1.14 (95% CI 0.80-1.63, p=0.453) Event free survival at 1 year (major amputation or reintervention): 65% vs 62% (p=0.381, bivariate) Multivariate HR 0.89 (95% CI 0.70-1.14, p=0.348)		
Bodewes 2018[25] Retrospective, NSQIP vascular-targeted files, U.S. ~ 83 centers 2011-2014	No specific definition other than the fact that they stratified into claudication and CLTI	First time infrainguinal bypass (excluded fem-tibial/pedal) N=2010 Mean age 68.4 58% Male 43% smoking 43% rest pain 57% tissue loss 29% BMI > 30 48% DM 25% renal insufficiency 8.7% dialysis	First time endovascular intervention N=1792 Mean age 70.1 54% male 30% smoking 33% rest pain 67% tissue loss 31% BMI > 30 60% DM 34% renal insufficiency	30 days, surgery vs EV Mortality: 2.2% vs 2.1% (p = 0.79, bivariate) MALE (major amputation, major graft revision, new bypass, thrombolysis/thrombectomy): 6.8% vs 7.5% (p = 0.43, bivariate) Major amp: 3.3% vs 4.6% (p = 0.04, bivariate) Minor amp: 4.8% vs 3.3% (p = 0.02, bivariate) MACE (MI, stroke, death): 4.7% vs 3.6% (p = 0.08, bivariate) Bleeding (transfusion or secondary procedure for bleeding): 17% vs 8.5% (p < 0.001, bivariate)	NA	Tibial vs fempop, only for procedure time

Author Year Population	**How was CLI defined?**	**Surgical intervention N Patient characteristics**	**Endovascular intervention N Patient characteristics**	**Short-term Outcomes**	**Long-term Outcomes**	**Stratification variables**
		83% HTN 52% CHF 14% COPD	13% dialysis 85% HTN 53% CHF 11% COPD	Readmission: 18% vs 17% (p = 0.50, bivariate) Reoperation: 17% vs 13% (p = 0.001, bivariate) Secondary revascularization: 3.1% vs 4.3% (p = 0.07, bivariate) Procedure Time: Median(IQR) 200 (150-267) vs 95 (67-137) minutes for fempop procedures (p < 0.001, bivariate); 243 (195-305) vs 92 (66-135) minutes for tibial procedures (p < 0.001, bivariate) LOS: Median(IQR) 6 (4-12) vs 2 (1-8) days (p < 0.001, bivariate) On multivariate analysis: EV was predictive of fewer MACE (OR 0.6; 95% CI = 0.4-0.9; p < 0.01), SSI (OR 0.1; 95% CI = 0.1-0.2; p < 0.001), bleeding (OR 0.4; 95% CI = 0.3-0.5; p < 0.001), reop (OR 0.7; 95% CI = 0.5-0.8; p < 0.001), secondary revasc (OR 1.6; 95% CI = 1.04-2.3; p = 0.03), unplanned readmission (OR 0.8; 95% CI = 0.7-0.9; p < 0.01); no difference mortality (OR 0.7; 95% CI = 0.4-1.1; p = 0.12), MALE (OR 1.0; 95% CI = 0.8-1.3; p = 0.89), major amputation (OR 1.1; 95% CI = 0.8-1.6; p = 0.58)		
Cejna 2011[31] Austrian single center retrospective study, abstract only	NA	"surgical" N = 50 extremities	"endovascular" N = 40 extremities	Initial costs, surgery vs EV: 15,416 euros vs 9,858; no p-value provided	No difference in limb salvage (p=0.62) or survival (p=0.24) between surgical and endovascular groups at 30 days, 1 year, 2 years, and 4 years	NA

Author Year Population	**How was CLI defined?**	**Surgical intervention N Patient characteristics**	**Endovascular intervention N Patient characteristics**	**Short-term Outcomes**	**Long-term Outcomes**	**Stratification variables**
					Total costs of follow-up, surgery vs EV, 27,429 vs 17,443, no p-value provided	
Darling 2017[26] Single center, US, 2005-2014	No specific definition	First time procedures, below iliacs N = 668 procedures 62% Male Mean age 70.8 68% h/o smoking 26% current smokers 23% rest pain 48% ulcer 30% gangrene 73% DM 17% dialysis	First time procedure, below iliacs, angioplasty with or without stenting N=668 procedures 56% Male Mean age 72.3 53% h/o smoking 16% current smokers 16% rest pain 57% ulcer 27% gangrene 76% DM 23% dialysis	Surgery vs EV 30-day partial foot/toe amp: 9% vs 14% , p<0.01, bivar) 30-day mortality: 3.3% vs 2.8% (p=0.63, bivariate) Hematoma 7.9% vs 4.2% (p<0.01, bivariate) LOS: total -- Mean 10 vs 7 days (p<0.001, bivariate); postop – mean 7 vs 5 days (p<0.001, bivariate)	Surgery vs EV Median 18 months bypass Median 14 months EV F/u included duplexes ultrasounds, ABI's, PVRs, toe pressures Complete wound healing at 6 months: 43% vs 36% (p<0.01, bivariate) Freedom from restenosis at 3 years (61% vs 45%, p<0.001, bivariate) PTA had multivariable HR of restenosis of 1.7 (95% CI 1.4-2.2) Freedom from reintervention at 3 years 62% vs 52% (p=0.04, bivariate) PTA had a multivariable HR of reintervention of 1.6 (95% CI 1.3-2.1) Primary patency at 3 years 72% vs 63%, (p=0.02, bivariate) PTA had multivariable HR of 1.5 (95% CI 1.1-2.1) Partial foot or toe amp 23% vs 30% (p<0.01, bivariate) Freedom from major amp at 6 months (93% vs 92%, p=0.88, bivariate) and 3 years (81% vs 85%, p=0.40, bivariate)	Stratified partial foot and toe amputation rates between indication (rest pain, ulcer, gangrene)

Author Year Population	**How was CLI defined?**	**Surgical intervention N Patient characteristics**	**Endovascular intervention N Patient characteristics**	**Short-term Outcomes**	**Long-term Outcomes**	**Stratification variables**
					Freedom from RAS (Reintervention, major amputation, restenosis) at 3 years: 47% vs 34%, P<0.001, bivariate PTA had multivariable HR of 1.7 (95% CI 1.3-2.2) Survival at 3 years (61% vs 52%, p<0.01, bivariate) PTA had multivariable HR of 1.4 (95% CI 1.1-1.8)	
Darling 2018[34] Single center, US, 2005-2014	Patients were "distinctly classifiable as chronic limb-threatening ischemia [including] tissue loss and rest pain"	Surgical bypass graft N=376 64% Male Mean age 69 100% DM 59% CAD 26% dialysis-dependent 21% current smoking Fem-pop TASC classification A 23% B 30% C 21% D 26%	Percutaneous transluminal angioplasty with or without stenting N=339 61% male Mean age 68 100% DM 55% CAD 28% dialysis dependent 14% current smoking Fem-pop TASC classification A 27% B 47% C 11% D 16%	Surgery vs EV Perioperative mortality 3.8% vs 3.0% (p=0.55) Acute kidney injury 19% vs 23% p=0.24 LOS 11 vs 8 days (p<0.001)	5-year Surgery vs EV MALE 45% vs 31% (p=0.29) Mortality 64% vs 71% (p=0.23) Major amputation 30% vs 26% (p=0.90) Reintervention 47% vs 58% (p<0.01) Reintervention, amputation, stenosis 67% vs 75% (p<0.001)	NA
Dayama 2019[35] Multi-center	Critical limb-threatening ischemia with	Surgical bypass N=534 71% male	Endovascular N=821 67% male	30 days, Surgery vs EV Mortality 3.2% vs 1.8% (p=0.1) MALE 9.0% vs 11.7% (p=0.19)	NA	NA

Author Year Population	How was CLI defined?	Surgical intervention N Patient characteristics	Endovascular intervention N Patient characteristics	Short-term Outcomes	Long-term Outcomes	Stratification variables
	infrageni-culate arterial disease	Mean age: 67 66% DM 24% current smoking 12% dialysis dependent	Mean age: 69 71% DM 13% current smoking 22% dialysis dependent	Transtibial or proximal amputation 4.3% vs 7.4% (p=0.02) LOS 11.87 vs 7.17 (p<0.01) Unplanned operation 19.1% vs 17.2% (p=0.36)		
Dosluoglu 2006[27] VA single center study	Rutherford 4-6	Lower extremity bypass N = 122 Only present demographics by time period, not by intervention	Percutaneous vascular intervention N = 105 Only present demographics by time period, not by intervention	30 days, Surgery vs EV All bivariate comparisons Mortality – 3.3% vs 1% (p=0.032, this is a comparison across 4 groups including hybrid and primary amputation) Mean LOS – 10.7 days vs 4.7 days (p<0.001)	24 months, Surgery vs EV: All bivariate comparisons Survival – 64% vs 56% (p=0.008, across 4 groups including hybrid and primary amputation) Limb salvage – 71% vs 83% (p=0.008, across 3 groups including hybrid) PP – 49% vs 56% (p=0.01, across 3 groups including hybrid) APP – 58% vs 79% (p=0.004, across 3 groups including hybrid) SP – 68% vs 88% (p=0.026, across 3 groups including hybrid)	NA
Dosluoglu 2012[28] VA single center study	Rutherford 4-6	Open bypass N = 138 Age = 69.2 40% diabetes 50% smoker 25% nonambul 62% CAD 79% HTN	Infrainguinal percutaneous vascular intervention N = 295 Age = 73.0 69% diabetes 28% smoker 30% nonambul 61% CAD 78% HTN	30 days, surgery vs EV Complications 29.1% vs 7.2% (p<0.001, bivariate) Mortality 6.0% vs 2.8% (p=0.079, bivariate) LOS 9.7±8.8 days vs 4.8±7.5 days (p<0.001, bivariate)	5 years, surgery vs EV Overall survival 46%±5% vs 36%±4% (p=0.146, bivariate) AFS 39%±5% vs 30%±3% (p=0.227, bivariate) Limb salvage 78%±4% vs 78%±3% (p=0.992, bivariate) PP 48%±6% vs 50%±5% (p=0.800, bivariate) APP 59%±6% vs 70%±5% (p=0.039, bivariate)	TASC D lesions

Author Year Population	How was CLI defined?	Surgical intervention N Patient characteristics	Endovascular intervention N Patient characteristics	Short-term Outcomes	Long-term Outcomes	Stratification variables
		17% cerebrovasc dz 74% HLD 28% COPD 8% dialysis N = 151 limbs 28% rest pain 39% ulcer 33% gangrene	8% cerebrovasc dz 69% HLD 21% COPD 10% dialysis N = 363 limbs 11% rest pain 47% ulcer 42% gangrene		SP 64%±6% vs 73%±6% (p=0.022, bivariate) Reintervention –23.7% vs 30.3% (p N/A)	
Gargiulo 2011[32] US single center, retrospective study, abstract only	Rutherford class 4 or 5	"open-only" N = 62	"endovascular-only" N = 57	Surgery vs EV, no statistics provided, all appear bivariate Mean LOS 10.4 days vs 9.3 days Cost of hospitalization $45,832 vs $49,802 Readmission within 90 days– 13% vs 12% Discharge to SNF 44% vs 35%	NA	NA
Kim 2012[33] Single site, retrospective, Conemaugh Memorial Medical Center in Johnstown, PA, abstract only	Not specified beyond "diagnosis of critical limb ischemia requiring revasculari-zation"	Conventional bypass surgery using vein graft N = 84	Atherectomy, balloon angioplasty, stent placement N = 130	1 month, 3 months, 6 months, EV vs surgery Amputation rate: 2.3%, 9.2%, 11.5% vs 3.6%, 6%, 7.2% (p = 0.671, bivariate) Reintervention rate: 5.4%, 10.8%, 14.6% vs 8.3%, 15.5%, 21.4% (p = 0.940, bivariate) Cost of first intervention: $27,365.03 ± $18,916.34 vs $24,727.99 ± $14,373.89 (p = 0.292, bivariate)	12 mo, 24 mo, <36 mo, EV vs surgery Amputation rate: 13%, 14.5%, blank vs 8.4%, 9.6%, 10.8% (p = 0.671, bivariate) Reintervention rate: 19.2%, 20%, 20.9% vs 27.4%, 28.6%, 29.7% (p = 0.940, bivariate) More than 2 interventions at 36 months: 4.6% vs 8.3% (p = 0.268, bivariate)	NA
Siracuse 2016[36]	Ischemic rest pain or tissue loss,	Lower extremity bypass N = 3059 pts	Percutaneous vascular intervention	30 days, EV vs surgery	3 years, EV vs surgery	Cohort II – patients without comorbidities

Author Year Population	How was CLI defined?	Surgical intervention N Patient characteristics	Endovascular intervention N Patient characteristics	Short-term Outcomes	Long-term Outcomes	Stratification variables
>300 hospitals in North America (3 cohorts: I – all patients II – patients without comorbidities increasing surgical risk III – patients with treatment limited to the SFA)	age 35+, excluded peripheral aneurysms, excluded hybrid procedures	Age = 68.1 62.1% male 56.2% diabetes 81.1% smoker 8.2% dialysis 18.1% CHF 24.1% COPD 70.3% ambulatory 62.3% tissue loss	N = 4838 pts Age = 70.7 56.5% male 68.0% diabetes 62.7% smoker 17.1% dialysis 25.9% CHF 20% COPD 62.2% ambulatory 76.6% tissue loss	Mortality – 2% vs 2.2% (p=0.69, bivariate) Multivariate OR 0.59 (95% CI 0.43-0.81, p=0.001, favors EV) Median LOS – 1 day vs 5 days (p<0.001, bivariate) Multivariate MR 0.52 (95% CI 0.50-0.55, p<0.001, favors EV)	Unadjusted survival 69.9% vs 77.8% (p<0.01, bivariate) Multivariate HR for death 1.23 (95% CI 1.07-1.42, p=0.003, favors surgery) Amputation/Death 1 yr – EV vs surgery HR 0.98 (95% CI 0.82-1.16, p=0.816, bivariate) MALEs/Death 1 yr – EV vs surgery HR 0.81 (95% CI 0.72-0.91, p<0.001, bivariate)	increasing surgical risk Cohort III – patients with treatment limited to the SFA)
Stoner 2008[21] Single center retrospective study	Rutherford class > 3	Open bypass using prosthetic conduit or vein graft N = 102	Angioplasty, stenting, atherectomy N = 86	Primary assisted patency at 12 months Open bypass 66% ± 0.05% Endovascular 54% ± 0.05% (p<0.01) Initial cost of index procedure: Open bypass $13,277±598 Endovascular $7,176±309 (p<0.001 for difference) Cost per patient-day of patency at 12 months from index procedure: Open bypass $210±80 Endovascular $359±143 (p = not significant for diff)	NA	NA
Taylor 2009[29] Single center retrospective study	Lower extremity ischemic tissue loss	Lower extremity bypass+Hybrid N = 361 60% male 67% diabetes 64% smoker 25% ESRD 58% CAD 60% ulcer 40% gangrene	Lower extremity angioplasty N = 316 51% male 68% diabetes 57% smoker 42% ESRD 66% CAD 63% ulcer 37% gangrene	NA	1 yr, surgery vs EV Composite (wound healing, limb salvage at 1 year, maintenance of amb status, survival for 6 months): 44.3% vs 37% (p=0.05, bivariate) Patency – 75.6% vs 69.9% (p=0.097, bivariate)	NA

Author Year Population	How was CLI defined?	Surgical intervention N Patient characteristics	Endovascular intervention N Patient characteristics	Short-term Outcomes	Long-term Outcomes	Stratification variables
					Wound healing – 47.4% vs 39.2% (p=0.033, bivariate)	
Tsai 2015[30] Clinical registry at Kaiser Permanente Colorado and KP Northern California, 2005-2011	Rest pain, tissue loss, or unspecified	N = 633 Mean age 72.2 56.4% male 21.0% current smoker 19.1% past MI 31.4% PCI or CABG 58.9% diabetes 34.6% stroke 33.2% CKD 31.3% CHF 94.9% HTN 30.0% COPD 84.4% HLD 54.0% prev ACS 13.0% dialysis 6.5% prev EV procedure 13.1% previous bypass	N = 291 Mean age 72.1 49.8% male 27.8% current smoker 18.2% past MI 28.9% PCI or CABG 53.3% diabetes 21.3% stroke 33.3% CKD 28.2% CHF 93.1% HTN 28.9% COPD 80.8% HLD 47.4% prev ACS 7.2% dialysis 6.5% prev EV procedure 3.1% previous bypass	EV vs surgery, CLI only 30-day complication rate 18.2% vs 40.6% RR 0.45 (95% CI = 0.35-0.58) (p < 0.001, bivariate) Intra-procedure complication 7.9% vs 4.0% RR 2.00 (95% CI = 1.16-3.47) (p = 0.01, bivariate) After procedure, predischarge 5.5% vs 22.9% RR 0.24 (95% CI = 0.15-0.39) (p < 0.001, bivariate) Postdischarge to 30 days 6.9% vs 20.5% RR 0.33 (95% CI = 0.21-0.52) (p < 0.001, bivariate)	EV vs surgery, CLI only Target lesion revasc 1 year 19.1% vs 10.8% HR 1.59 (95% CI = 1.05-2.40) (p N/A, bivariate) 3 years 31.6% vs 16.0% HR 2.38 (95% CI = 1.74-3.24) (p N/A, bivariate) All years (5.5 years) 37.3% vs 22.2% HR 2.29 (95% CI = 1.69-3.12) (p N/A, bivariate) Target limb revasc 1 year 26.5% vs 13.4% HR 1.62 (95% CI = 1.13-2.32) (p N/A, bivariate) 3 years 38.9% vs 21.0% HR 2.09 (95% CI = 1.58-2.77) (p N/A, bivariate) All years (5.5 years) 50.7% vs 30.4% HR 2.17 (95% CI = 1.65-2.84) (p N/A, bivariate) Major amputation 1 year 15.5% vs 18.6%	NA

Author Year Population	**How was CLI defined?**	**Surgical intervention N Patient characteristics**	**Endovascular intervention N Patient characteristics**	**Short-term Outcomes**	**Long-term Outcomes**	**Stratification variables**
					HR 0.84 (95% CI = 0.58-1.23) (p N/A, bivariate) 3 years 21.2% vs 25.4% HR 0.84 (95% CI = 0.60-1.17) (p N/A, bivariate) All years (5.5 years) 28.1% vs 32.2% HR 0.95 (95% CI = 0.71-1.29) (p N/A, bivariate) Minor amputation 1 year 13.9% vs 19.0% HR 0.64 (95% CI = 0.42-0.98) (p N/A, bivariate) 3 years 17.9% vs 22.2% HR 0.80 (95% CI = 0.55-1.15) (p N/A, bivariate) All years (5.5 years) 21.2% vs 23.9% HR 0.82 (95% CI = 0.57-1.17) (p N/A, bivariate) Death 1 year 13.4% vs 19.3% HR 0.64 (95% CI = 0.44-0.92) (p N/A, bivariate) 3 years 26.9% vs 35.9% HR 0.63 (95% CI = 0.47-0.84) (p N/A, bivariate) All years (5.5 years) 43.5% vs 52.6% HR 0.75 (95% CI = 0.59-0.95) (p N/A, bivariate)	

Author Year Population	**How was CLI defined?**	**Surgical intervention N Patient characteristics**	**Endovascular intervention N Patient characteristics**	**Short-term Outcomes**	**Long-term Outcomes**	**Stratification variables**
					(mortality differences not significant on propensity-matched sensitivity analysis)	

APPENDIX H. CITATIONS FOR EXCLUDED PUBLICATIONS

Did not present CLI data separately (n=43)

1. Cambou JP, Aboyans V, Constans J, Lacroix P, Dentans C, Bura A. Characteristics and outcome of patients hospitalised for lower extremity peripheral artery disease in France: the COPART Registry. *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery.* 2010;39(5):577-585.
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Background/other (n=25)

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Outcome (n=11)
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Systematic review (n=3)

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Sample size <500 (n=2)

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No utilization measure (n=1)

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<u>Lack of sufficient clinical data (n=13)</u>

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