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The Use of Cost Effectiveness Analysis for Critical Limb Ischemia: Systematic Literature Review

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Abstract

Background: There is limited knowledge about the utilization of cost effectiveness analysis (CEA) for the value assessment of Medical Devices (MDs) in the field of Critical Limb Ischemia (CLI). The objective of this study was two-fold. First, it was to provide relevant insight into the state of the art with respect to the use of CEA in the field of CLI. Second, it was to critically appraise the quality of included studies.

Methods: Literature search in Scopus, Science, and Pubmed databases was performed following PRISMA guidelines. Drummond and Jefferson's (1996) checklist modified by Zelle and Baltusen (2013) was adopted to critically appraise included CEAs. First, each study was evaluated across all checklist's items (individual appraisal). Second, each item was evaluated separately across all included studies (group appraisal).

Results: Out of 340 publications, 18 studies met the inclusion criteria. The most common comparison was bypass against angioplasty. ICER differed from $2455 per QALY for the cool excimer laser-assisted angioplasty against Tibial Balloon Angioplasty (TBA) in Canada to $15,403 per additional year of ambulation for purely endovascular against local wound care alone in the USA. The individual appraisal of included CEAs revealed that the quality varied widely from 42% to 87% of maximum score. The group appraisal highlighted three key methodological deficiencies: (1) the gaps in the sourcing of cost data, (2) short time horizon of the analysis, and (3) the limitation of study results generalizability due to numerous settings' specific determinants such as multiple comparisons.

Conclusions: The results of studied CEAs varied widely, which can be attributed to the great number of alternative treatment options for limb ischemia and heterogeneity of studied population. Future MDs value assessment guidelines should focus on the greater transparency and robustness in the use of real-world data for both costs and treatment effect estimation.

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Introduction

The increase in average life expectancy in OECD countries by more than 12 years in the last half a century has amplified the pressure on healthcare systems to ensure sufficient access to medical services for the aging population [1]. Across all fields of innovation, healthcare outpaces other sectors, with the greatest number of patents granted for medical technologies in recent years [2]. To strike a balance between limited healthcare resources and growing healthcare needs, policymakers are expanding the role of Cost Effectiveness Analysis (CEA) in their decision-making processes. CEA has become a recognized tool in the search for the optimal allocation of limited healthcare budgets [3]. It provides the framework to study all economic consequences of the implementation of a given health technology to clinical practice. So far, CEA has been predominantly used in the support of pricing and reimbursement of pharmaceuticals.

However, today there is a growing recognition of the importance of CEA in decision-making processes even beyond pharmaceuticals. Still, there is a limited number of jurisdictions that adopt CEA to the pricing and reimbursement of MDs. Some experts claim that key differences between drug and non-drug technologies make the economic evaluation of the former more challenging. Among key constraints, experts usually mention the lack of randomized controlled trial, the heterogeneity of patients' groups, and the impact of end users' learning curve on treatment outcomes. Therefore, it is interesting to investigate the methodological robustness of economic assessments of medical devices and ask the question whether there is any need to develop any specific guidelines for the value assessment of MDs.

The chosen scope of analysis was Critical Limb Ischemia (CLI). This represents the end-stage of Peripheral Artery Disease (PAD), associated with the highest mortality rates among all forms of occlusive vascular disease [4]. CLI is also related to poor quality of life and high treatment costs [4]. In the USA, PAD has the third-largest prevalence among other major diseases with the total costs of up to 389 billion dollars in 2015, which is far higher than any other diseases such as diabetes, coronary artery disease, and cancer [5]. There are several treatments for CLI, such as endovascular revascularization, bypass surgery, amputation, and local wound care.

The objective of this study was two-fold. First, it was to perform a systematic literature review of available Cost Effectiveness Analysis (CEA) of MDs in the field of Critical Limb Ischemia (CLI). Second, it was to critically appraise included studies and verify whether any methodological challenges affecting their quality are needed to be considered by the future researchers interested in economic evaluation of new modalities for the treatment of CLI and even other therapeutic areas.

Materials and methods

Literature search

Literature search in Scopus, Science, and Pubmed databases was performed. The following keywords were selected: "chronic limb ischemia," "Endovascular limb," "thrombosis limb," "vascular limb," and "cost-effectiveness." Given the rapid advancement of medical technologies, the time framework for the search was limited to the period from January 2007 to January 2019. Only publications written in English including both costs and health outcomes were selected. First, two reviewers (SMS and KK) independently assessed abstracts and, then, full texts to ensure the eligibility of all included studies. All disagreements were resolved through discussion to reach consensus. PRISMA guidelines were followed. This research did not involve human or animal subjects or patients, thus the authors did not require to provide Institutional Review Board (IRB) approval.

Critical appraisal

Drummond and Jefferson's checklist modified by Zelle and Baltusen (2013) was adopted to critically appraise included CEAs [6,7]. It consists of 30 items grouped into five domains: study design, effectiveness, cost estimation, analysis, and results interpretation.

The authors scored each item based on Gerard scoring [8]. The scale ranged from 0="item is neither considered nor described" through 1="item is considered but not described" to 2="item is fully considered and described." A response of "not applicable" was recorded if a particular item was not relevant to the study [8].

The maximum number of points was 60. However, if any specific item was not applicable (N/A), the maximum obtainable score was reduced by two points per item (see Table V. Critical Appraisal) [6]. The scoring was used in two ways: individual and group appraisal.

Individual appraisal

Each publication was categorized in one of the three groups of "High," "Midrange," and "Low" score. The study received a high score if at least 42 out of 60 points was granted (i.e. above 70% of the maximum score). A study was in midrange score with 30–41 points and in low score with less than 30 points (i.e. below 50% of maximum score).

Group appraisal

Each item of the checklist was given an average score for the group of all studies included in the systematic literature review. It was based on the mean of individual scores assigned to each CEA. Given the adaptation of Gerard scoring, the mean score could be ranged from 0 (when missed) to 2 (fully considere0.

Results

In total, 340 publications were identified. After the duplication removal (22), 268 articles were excluded in the process of the abstract screening. In that group, there were non-peer-reviewed book chapters (n=5); studies without abstracts (n=21); non-English (n=2); or, out of scope with different indication and/or without economic analysis (n=240). After abstract screening, the total of 50 articles was included for full-text review. Finally, 18 publications were included (see Figure 1. The flow diagram of systematic literature review) [9-26].

Study characteristic

The majority of included studies used the perspective of the United States of America (n=9). The remaining ones related to Canada (n=2), the United Kingdom (n=2), Ireland (n=2), Greece (n=1), and Italy (n=1) (Table I. Characteristics of included studies).

Out of 18 publications, only seven defined the target population with grading of commonly established clinical classification systems such as Ruthord and TASC II (Table I. Characteristics of included studies).

The clinical data were sourced from prospective studies (n=8) out of which six used randomized control trials (RCTs). The meta-analysis (n=5) or retrospective data (n=4) as well as the synthesis of literature findings (n=1) were utilized in the remaining ones (Table I. Characteristics of included studies).

While eight publications compared two treatment modalities, other studies used multiple options. The most common comparison was bypass against angioplasty (Table II. Key characteristics of cost effectiveness analysis studies).

The rate of amputation and mortality were the frequently adopted health outcomes. The ambulatory ability and the risk of revascularization were relatively common too (Table II. Key characteristics of cost effectiveness analysis studies).

Multiple treatment outcomes were chosen in nine cases. In ten studies, QALY based approach was chosen which was complemented by additional endpoints in five cases.

The Markov model was adopted six times, a decision tree was used in three studies and discrete event simulation was used once. In seven cases, modeling approach to the cost effectiveness analysis was not specified (Table II. Key characteristics of cost effectiveness analysis studies). The time horizon varied from one to ten years. Most studies applied a 3.5% discount rate.

The lowest ICER (2,073€ ($2,455) was determined for the comparison of Cool Excimer Laser-Assisted Angioplasty (CELA) against Tibial Balloon Angioplasty (TBA) in the Canada settings. It was a study conducted in the group of patients with critical limb ischemia with TASC II type C and D lesion. The highest ICER ($15,403) as established for purely endovascular against local wound care alone in the USA settings among End-Stage Renal Disease (ESRD) patients who have non healing ulcers associated with severe PAD (ie, Rutherford category 5 ischemia) (Table III. Results of cost effectiveness analysis).

Study quality

In total, 18 publications were appraised with the Zelle and Baltusen checklist [6]. The individual appraisal of included studies revealed that eight out of 18 publications ranked with the highest score. At the same time, five received "mid" and five "low" score. The highest scores were granted to Simpson et al. 2014, Barshes et al. 2012, and Bradburry et al. 2010 [9,12,3]. Meanwhile, publications of Werneck et al. 2009 and Sultan et al. 2011 received the lowest number of points (Table IV. Scoring of critical appraisal) [18,22].

The group appraisal revealed that the most consideration was given to the "interpretation of results" domain (the average score of 1.6) and the least to "cost estimation" (the average score of 0.6) (Table V. Critical Appraisal).

Across all items included in the "study design" domain, the perspective of analysis received the lowest attention (average score of 0.6), while the description of the research question was addressed by all authors (average score of 2.0). In the "effectiveness" domain, the methods of evidence synthesis received the lowest appraisal grade (average score of 1.5). On the other hand, there were limited challenges with the presentation of primary outcome measure of the analysis which was discussed in all publications (average score of 2.0). In the "cost estimations" domain, apart from the description of choice of currency (average score of 1.2), there were no items adequately covered. The appraisal revealed that little attention was given to the separation of healthcare resources utilization and unit costs (average score of 0.2). In the "analysis" domain, all items were poorly deliberated across 18 studies. On average, the choice of discount rates was least discussed (average score of 0.8). Only time horizon of the analysis and details of model was moderately covered (average score of 1.7). Finally, the "interpretation of results" happened across all studies with the highest and lowest average score given towards the conclusions (average score of 2.0) and the choice of major outcome (average score of 0.4) respectively.

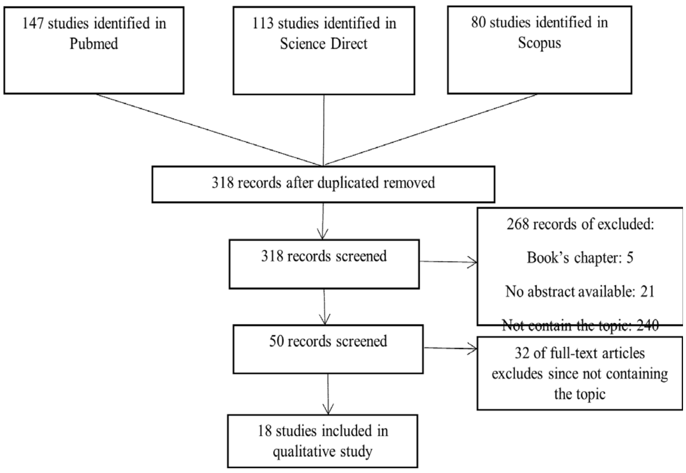

Figure 1: The flow diagram of systematic literature review.

Table 1: Characteristics of included studies.

Author	Jurisdiction	Publish year	Population	Comorbidities	Source of data
Barshes N et al	USA	2013	chronic limb ischemia whom an endovascular option of revascularization did not exist.	N/A	Meta-analysis of three RCTs (PREVENT IIII, Circulase I and II trials,BASIL), observational data
Barshes N et al	USA	2012	CLI with tissue loss (Rutherford category 5 limb ischemia)	N/A	Meta-analysis of three RCTs (PREVENT IIII, CirculaseIandIItrials, BASIL), observational data
Bradbury AW et al	UK	2010	Severe limb ischemic and require immediate/early revascularisation.	N/A	Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial

Salisbury A et al	USA	2016	moderate to severe intermittent claudication or ischemic rest pain (Rutherford 2–4) and stenosis of 70% to 99% with lesion lengths between 4 and 18 cm or occlusion with lengths of ≤10 cm	N/A	Multicenter RCTs of the IN.PACT Admiral DCB versus standard PTA (IN.PACT SFA trial)
Vaidya V et al.	USA	2016	Non-embolic acute limb ischemia	N/A	Retrospective analysis of hospital database (205 pts)
Barshes N et al	USA	2014b	PAD (Rutherford category 5) with non-healing wounds	End stage renal disease	Meta-analysis of single center studies, multi-institution observational studies, large clinical database (Vascular Study Group of New England and American College of Surgeons National Surgical Quality Improvement Project)
Barshes N et al	USA	2014c	CLI with a prior major amputation of the contralateral lower limb	age >80 years old, poorer post-operative clinical and functional outcomes	Meta-analysis of RCTs (BASIL, PREVENT III) and large observational series
Werneck et al	Canada	2009	CLI	High risk for surgery based on their comorbidities using the American Society of Anesthesiologist Scoring Physical Status Classification System (ASA>=3)	Retrospective data (patient who are referred to Toronto Hospital from January 1, 2001, to March 31, 2007
Palena et al	Italy	2016	CLI (Rutherford 4-6) with transcutaneous partial pressure of Oxygen <=30 mmHg, which referred to endovascular therapy, without iliac disease, and with femoropopliteal chronic total occlusions at least 15 cm in length (TASC II C-D)	N/A	Prospective, single centre, single arm study
Forbes et al	UK	2010	Severe ischemia of the leg	N/A	Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial
Lurie et al	Ohio, USA	2015	Non-embolic acute limb ischemia	arterial hypertension, coronary artery disease, diabetes, chronic obstructive pulmonary disease, chronic kidney disease, chronic peripheral arterial disease	Promedica Community Hospital Databases 2009-2012
Sultan et al	Ireland	2011	Critical limb ischemia (Rutherford >= 4)	non-reconstructible arterial disease, diabetes mellitus, hypertension ischemic heart disease, dyslipidemia, renal impairment, smoking, hyperhomocysteinemia	Prospective, database in tertiary referral center 2004-2009
Sridharan et al.	Pittsburgh, USA	2017	Superficial femoral artery disease	N/A	Literature review
Sultan et al	Ireland	2009	Critical limb ischemia with TASC II type C and D	Diabetes, smoking, heart disease, renal insufficiency, comorbidity severity sources	Prospective, database in tertiary referral center 2002-2007
Sultan et al	Canada	2013	Critical limb ischemia with TASC II type C and D lesion	diabetes mellitus, hypertension, Hyperlipidemia, renal insufficiency, smoking, homocysteinemia, ischemic heart disease	Prospective, VascuBase, Canada, 2005-2010
Jaff et al	Massachusetts, USA	2010	Peripheral arterial disease	Diabetes Mellitus	Retrospective, 5% Medicare Standard Analytic Files
Simpson et al	N/A	2014	Symptomatic PAD undergoing endovascular treatment for disease distal to the inguinal ligament.	N/A	Meta-analysis
Katsanos et al	Greece	2013	Critical limb ischemia	N/A	Single-center, prospective, controlled studies

Table 2: Key characteristics of cost effectiveness analysis studies.

No	Study	Intervention compared	Currency, year	Outcome measures	Perspective	Time horizon	Dis-count-ing	Type of model
1	Simpson et al	1. Paclitaxel-coated balloons 2. PTA with bail-out paclitaxel-eluting stents 3. BMSs (bare-metal stent) 4. Paclitaxel-eluting stent 5. PTA with bail-out BMSs 6. Stent-graft 7. EVBT (endovascular brachytherapy0 8. PTA, no bail-out stenting 9. Cryoplasty	£, 2009-2010	QALY	NHS and personal social service	100 years	3.5%	Discrete-event simulation model
2	Katsanos et al	1. Bail-out use of Sirolimuseluting stents 2. Bare metal stents after suboptimal balloon angio-plasty (Bail-out SES)	EUR	Event-free life-year gained	NA	3 years	NA	Simplified cost-effectiveness analysis
3	Barshes N et al 2013	1. conservative therapy (local wound care, amputa-tion as needed); 2. primary amputation; 3. bypass with autologous alternative vein (AAV), including arm or lesser saphenous vein; 4. bypass with GSV <3 mm in diameter; 5. bypass with polytetrafluoroethylene (PTFE); 6. cryopreserved venous allograft 7. cryopreserved arterial allograft.	USD, 2011	Ambulatory ability	societal	10 years	3.50%	Markov model
4	Barshes N et al 2012	1. Local wound care 2. Primary amputation, 3. Bypass with surgical revision(s) 4. Bypass with endovascular revisions 5. Purely endovascular, 6. Endovascular, bypass for failure	USD, 2009	QALY	societal	10 years	3.50%	Markov model
5	Bradbury AW et al 2010	1. Bypass 2. Angioplasty	UK pounds, 2006/07	AFS, OS QALY	healthcare system	3 years 7 years	3.50%	Cost - effective-ness
6	Salisbury A et al 2016	1. drug-coated balloon (DCB) angioplasty 2. Angioplasty	USD, 2014	QALY	Healthcare system	2 years	NA	Markov model
7	Vaidya V et al. 2016	1. Catheter-directed thrombolysis (CDT) alone 2. CDT followed by angioplasty 3. Open surgery, such as operative thrombectomy, endarterectomy, patch angioplasty, bypass, or any combination 4. Endovascular (EV) procedures (atherectomy, balloon angioplasty, thrombectomy with angiojet, stenting, and their combinations) 5. Hybrid	USD, not stated	Mortality Life years gained	NA	3 years	NA	Decision tree
8	Barshes et al 2014b	1. Local wound care, with selective major amputa-tion as indicated; 2. Primary major amputation 3. Revascularization with bypass using an autologous vein conduit and subsequent endovascular interven-tion as needed 4. Revascularization with infra-inguinal surgical bypass using an autologous vein conduit and open surgical intervention 5. Initial revascularization with endovascular inter-vention with surgical bypass for failure of wound healing; possible endovascular revisions; 6. Revascularization achieved purely through an initial endovascular intervention, then subsequent additional endovascular reinterventions as needed.	USD, 2011	all-cause mortal-ity major ampu-tation	Societal	10 years	3.50%	Markov model
9	Barshes et al 2014c	1. Endovascular revascularization or surgery 2. Local wound care alone or primary amputation	USD, 2011	Ambulatory abil-ity, Years of limb salvage, QALY.	NA	10 years	3.50%	Markov model

10	Werneck et al. 2009	1. Tibial Angioplasty 2. Surgery	USD	Freedom from major amputation OS Recurrence	NA	2 year	NA	NA
11	Palena et al. 2016	1. SUPERA stenting 2. Angioplasty	EUR, not stated	Freedom from target lesion revascularization	NA	1 year	NA	NA
12	Forbes et al. 2010	1. Bypass surgery 2. Balloon angioplasty	USD, 2006	QALY	NA	3 years	3.50%	NA
13	Lurie et al. 2015	1. Cathether directed thrombolysis 2. Catheter directed thrombolysis with angioplasty 3. Open surgery 4. Endovascular 5. Hybrid	USD, 2012	Amputation-free survival, re-admission free survival	NA	3 years	NA	Decision tree
14	Sultan et al. 2011	1. Pre and post Sequential compression biomechanical device (SCBD) 2. Amputation	EUR, not stated	QALY, Q-TWiST	NA	4 years	NA	NA
15	Sridharan et al. 2017	1. DCB, drug-eluting stent (DES), 2. Plain old balloon angioplasty (POBA) 3. Bare-metal stent (BMS).	USD, not stated	Patent limb at 1 year	payer	12 months	NA	Decision tree
16	Sultan et al. 2009	1. Subintimal angioplasty (SIA) 2. Bypass graft/Dynaflo ringed polytetrafluoroethylene graft	EUR, not stated	QALY Q-TWiST	NA	5 years	NA	NA
17	Sultan et al. 2013	1. Cool excimer laser-assisted angioplasty (CELA) 2. Tibial balloon angioplasty (TBA)	EUR, not stated	QALY Q-TWiST	NA	3 years	NA	NA
18	Jaff et al. 2010	1. Percutaneous transluminal angioplasty and stents 2. Stents only 3. PTA alone	USD, not stated	Mortality, Amputation, New clinical symptoms related to PAD	NA	6 years	NA	NA

Abbreviations: AFS: Amputation-Free Survival; OS: Overall Survival; Q-TWiST: Quality Time Spent Without Symptoms of Disease or Toxicity of Treatment.

Table 3: Results of cost effectiveness analysis.

No	Study	Time horizon	Discounting	Cost-effectiveness results
1	Simpson 2014	100 years	3.50%	Paclitaxel-coated balloons had the lowest cost and highest QALY against other interventions. (No ICER provided) (Min: cost: 49,890£, QALY: 3.402 - Paclitaxel-coated balloons; Max: cost: 58,097 QALY: 3.003 -Cryoplasty)
2	Katsanos 2013	3 years	NA	Bail-out SES had lower cost per event free life years gained against bare metal stents after suboptimal balloon angioplasty. The cost per additional event free life years gained = 6,518€
3	Barshes 2013	10 years	3.50%	Bypass with PTFE had higher ambulatory years ability against conservative therapy. The cost per additional ambulatory years ability = $5325
4	Barshes 2012	10 years	3.50%	Bypass with endovascular revision had the lowest cost per QALY against local wound care (compared to other interventions). (Min ICER = $47,735- Bypass with endovascular revision, Max ICER= 121,010 - Purely endovascular)
5	Bradbury 2010	3 years	3.50%	Bypass had lower cost per QALY against angioplasty. The cost per additional QALY = £134,257
		7 years		Bypass had lower cost per QALY against angioplasty. The cost per additional QALY = £41,401
6	Salisbury 2016	2 years	NA	DCB angioplasty had lower cost and more QALY against standard PTA (save $576) (No ICER provided)
7	Vaidya 2016	3 years	NA	Endovascular had the lowest ICER against surgery (compared to other interventions) (Min ICER: $4,609.23- EV, Max ICER: $54,837.5 - CDT)
8	Barshes 2014b	10 years	3.50%	Purely endovascular intervention had the lowest cost per additional year of ambulation against local wound care alone (compared to other interventions). The cost per additional year of ambulation: $15,403 -Purely endovascular
9	Barshes 2014c	10 years	3.50%	Revascularization strategies had lower long-term cost and more health benefits against primary amputation or wound care alone (No ICER provided)
10	Werneck 2009	2 year	NA	Tibial angioplasty had lower cost and number of LOS against surgery. The cost for tibial angioplasty $2,910.6 against surgery for $17,703.5 (No ICER provided)

11	Palena 2016	1 year	NA	SUPERA stenting had higher number of freedom from target lesion revascularization and lower cost against angioplasty. The cost for SUPERA Stenting for €4427.3 against angioplasty for €9564.9 (No ICER provided)
12	Forbes 2010	3 years	3.50%	BSX had higher cost per HRQoL against BAP. The cost per additional HRQoL : $184,492
13	Sultan 2011	3 years	NA	CDT had the higher cost per number of reintervention against open surgery (No ICER provided)
14	Sridharan 2017	4 years	NA	The cost per quality-adjusted life year of Sequential compression biomechanical device (SCBD): €2,953 (No comparator provided)
15	Sultan 2009	12 months	NA	DCB had the lowest overall cost per patency rates (most cost-effective) (Min ICER: $14,136-DCB, Max ICER: $87,377 - DES)
16	Sultan 2013	5 years	N/A	SIA had lower cost per QALY against bypass. The cost for SIA 5,663 € against bypass graft for 9,172 € (No ICER provided)
17	Jaff 2010	3 years	NA	CELA had the higher QALY against TBA. The cost per additional QALY: 2,073.10 €
18		6 years	NA	Percutaneous transluminal angioplasty (PTA) or atherectomy and stents had the lowest hazard ratio (HR) against other interventions. (No ICER provided) (Min HR: 0.829 - PTA or atherectomy and stents, Max HR: 1.720 - Wound care and surgical procedures) PTA and stents had the lowest risk-adjusted cost against other interventions. (Min cost: $15,197 - PTA and stents, Max cost: $41,214 - Wound care and surgical procedures)

Table 4: Scoring of critical appraisal

Publications	Variable	Study design	Effectiveness estimation	Cost estimation	Analysis	Interpretation of the result	Number of item scored	Sum of score	Total average score	Quality score
Simpson et al. 2014	Score granted	14	8	2	16	10	29	50	1.69	86%
	% domain score	100%	100%	25%	89%	100%				
Katsanos et al 2013	Score granted	10	4	1	10	10	29	35	1.21	60%
	% domain score	71%	50%	13%	56%	100%				
Barshes et al. 2013	Score granted	12	5	4	15	8	29	44	1,52	76%
	% domain score	86%	63%	50%	83%	80%				
Barshes et al. 2012	Score granted	14	7	4	17	8	29	50	1,72	86%
	% domain score	100%	88%	50%	94%	80%				
Bradburry et al.2010	Score granted	12	8	3	14	10	27	47	1,74	87%
	% domain score	86%	100%	38%	100%	100%				
Salisbury et al. 2016	Score granted	9	8	2	11	8	29	38	1,31	66%
	% domain score	64%	100%	25%	61%	80%				
Vaidya et al. 2017	Score granted	10	6	1	13	8	29	38	1,31	66%
	% domain score	71%	75%	13%	72%	80%				
Barshes et al. 2014b	Score granted	10	8	6	16	8	29	48	1,66	83%
	% domain score	71%	100%	75%	89%	80%				
Barshes et al. 2014c	Score granted	12	8	5	16	8	29	49	1,69	84%
	% domain score	86%	100%	63%	89%	80%				
Werneck et al. 2009	Score granted	4	8	3	1		23	22	0,95	48%
	% domain score	50%	100%	38%	0%	75%				
Palena et al. 2016	Score granted	4	8	0	3	6	20	21	1,05	53%
	% domain score	50%	100%	0%	30%	100%				
Forbes et al. 2010	Score granted	7	8	3	14	8	27	40	1,48	74%
	% domain score	50%	100%	38%	100%	80%				
Lurie et al. 2015	Score granted	10	7	2	3	7	29	29	1,00	50%
	% domain score	71%	88%	25%	17%	70%				
Sultan et al. 2011	Score granted	4	7	2	1	6	24	20	0,83	42%
	% domain score	50%	88%	25%	7%	60%				

Sridharan et al. 2017	Score granted	11	6	2	14	8	26	41	1,58	79%
	% domain score	79%	75%	25%	100%	100%				
Sultan et al. 2009	Score granted	9	8	4	7	8	27	36	1,33	67%
	% domain score	64%	100%	50%	50%	80%				
Sultan et al. 2013	Score granted	8	8	1	6	7	27	30	1,11	56%
	% domain score	57%	100%	13%	43%	70%				
Jaff et al. 2010	Score granted	8	8	0	3	8	27	27	1,00	50%
	% domain score	57%	100%	0%	21%	80%				
Total average domain score		70%	90%	31%	61%	83%				

Table 5: Critical Appraisal.

Item	Simpson 2014	Katsanos 2013	Barshes 2013	Barshes 2012	Bradburry 2010	Salisbury 2016	Vaidya 2017	Barshes 2014b	Barshes 2014c	Werneck 2009	Palena 2016	Forbes 2010	Lurie 2015	Sultan 2011	Sridharan 2017	Sultan 2009	Sultan 2013	Jaff 2010	Average score
Study design																			1.4
The research question is stated	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2.0
The economic importance of the research question is stated	2	2	2	2	2	2	2	2	2	2	0	2	2	2	2	2	2	2	1.9
The viewpoint(s) of the analysis are clearly stated and justified (relating to a particular decision-making context)	2	1	2	2	2	0	0	0	0	0	0	0	0	0	2	0	0	0	0.6
The rationale(s) for choosing the alternative programs or interventions which are compared is stated	2	2	2	2	2	2	2	2	2	NA	NA	0	2	NA	2	2	1	2	1.8
The alternatives being compared are clearly described	2	1	0	2	2	0	0	2	0	NA	NA	0	2	NA	0	2	2	0	1.0
All relevant alternatives are included	2	2	2	2	1	1	2	2	2	NA	NA	1	2	NA	2	1	1	2	1.7
The choice of economic evaluation is justified in relation to the questions addressed	2	0	2	2	1	2	2	2	2	0	2	2	0	0	1	0	0	0	1.1
Effectiveness estimation																			1.8
The primary outcome measure for the economic evaluation is clearly stated	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2.0
The source(s) of effectiveness estimates used is clearly stated	2	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1.9
Details of the design and results of the effectiveness study are given (if based on a single study)	NA	2	NA	NA	2	2	2	NA	NA	2	2	2	1	2	NA	2	2	2	1.9
Details of the methods of synthesis or meta-analysis of estimates are given (if based on multiple studies)	2	NA	0	1	NA	NA	NA	2	2	NA	NA	NA	NA	NA	2	NA	NA	NA	1.5
Data and methods used to value health states and other benefits are stated and justified.	2	0	1	2	2	2	0	2	2	2	2	2	2	1	0	2	2	2	1.6
Cost estimation																			0.6
Indirect non-healthcare costs are included or discussed	0	0	2	1	0	0	0	2	2	0	0	1	0	0	0	1	0	0	0.5
Quantities of resources are reported separately from their unit costs	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	2	0	0	0.2
Methods for the estimation of quantities and unit costs are described and justified.	2	0	0	1	1	0	1	1	2	1	0	0	0	0	0	1	1	0	0.6
Details of currency of price adjustments for inflation or currency conversion are given	0	1	2	2	2	2	0	2	2	2	0	2	2	0	2	0	0	0	1.2
Analysis																			1.3
Time horizon of costs and benefits are stated	2	2	2	2	2	2	2	2	2	1	1	2	1	1	2	2	1	1	1.7
Details of any model used are given	2	0	2	2	NA	2	2	2	2	NA	NA	NA	1	NA	2	NA	NA	NA	1.7
The choice of model used and the key parameters on which it is based are justified	2	0	1	2	NA	0	2	1	2	NA	NA	NA	0	NA	2	NA	NA	NA	1.2
The discount rate(s) is stated	2	0	2	2	2	0	0	2	2	0	NA	2	0	0	NA	0	0	0	0.9
The choice of rate(s) is justified	0	0	2	2	2	0	0	2	2	0	NA	2	0	0	NA	0	0	0	0.8

Details of statistical tests and confidence intervals are given for stochastic data	2	2	0	1	2	2	1	2	0	0	2	2	1	0	2	1	1	2	1.3
Sensitivity analysis is performed: 2) Probabilistic (bootstrap/Monte Carlo) 1) Deterministic (one way /multiple way)	2	2	2	2	2	2	2	2	2	0	0	2	0	0	2	1	1	0	1.3
The choice of variables in sensitivity analysis and the range over which these variables are varied is justified	2	2	2	2	2	2	2	2	2	0	0	2	0	0	2	1	1	0	1.3
Incremental analysis is performed and reported	2	2	2	2	2	1	2	1	2	0	0	2	0	0	2	2	2	0	1.3
Interpretation of results																			1.6
Major outcomes are presented in a disaggregated as well as aggregated form	2	2	0	0	2	0	0	0	0	0	NA	0	0	0	NA	0	0	0	0.4
The answer to the study question is given	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	1.9
Relevant alternatives are compared	2	2	2	2	2	2	2	2	2	NA	NA	2	2	0	2	2	2	2	1.9
Conclusions follow from the data reported	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2.0
Conclusions are accompanied by the appropriate caveats such as generalizability, equity, feasibility, and implementation	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1.9
Total	50	35	44	50	47	38	38	49	48	22	21	40	29	20	41	36	30	27	36.9

Discussion

Due to the scarce healthcare resources, budget holders are more and more interested in clinical and economic evaluation of medical devices. The objective of our study was twofold. First, it was to systematically review the state of the art regarding the utilization of cost effectiveness in the field of critical limb ischemia. Second, it was to critically appraise the quality of included studies.

Critical limb ischemia was chosen for the scope of the analysis because of its high morbidity and mortality rates.

Overall conclusion is that there was a significant diversity in the results of cost effectiveness analysis. For example, ICER differed from €2073.10 per QALY, for cool excimer laser-assisted angioplasty (CELA) against Tibial Balloon Angioplasty (TBA) to $15,403 per year of ambulation, for purely endovascular against local wound care. Such a wide variation may be attributed to at least two aspects.

First, it might be related to the great heterogeneity of patient's characteristics across the included studies. In the non-embolic Acute Limb Ischemia (ALI) group, endovascular treatment had lower cost per life years gained against surgery procedure, albeit open surgery was more cost-effective than Catheter-Directed Thrombolysis (CDT) [15,21]. Meanwhile, for limb ischemia patients with end-stage renal disease, purely endovascular intervention had the lowest cost per additional year of ambulation against local wound care alone with $15,403 per year of ambulation [16].

Second, the choice of alternative treatment options might play a role in the observed variation in the results of cost effectiveness analysis across included studies. For example there were three publications comparing economic consequences of procedures in the patients' grouped in the TASC II type C and D [19,24,25]. The 'SUPERA' stenting turned out to be more cost-effective than angioplasty, even though sub intimal angioplasty was more cost-effective against bypass [19,20]. At the same time, a Cool Excimer Laser-Assisted Angioplasty (CELA) had more QALY gains than Tibial Balloon Angioplasty (TBA) [25]. Still angioplasty turned out to be more preferable option for CLI patients who cannot undergo treatment as having less Length Of Stay (LOS) and less hospital cost than surgical procedure, despite the fact that bypass with polytetrafluoroethylene was the most cost-effective treatment if compared to conservative therapies [18,11].

The critical appraisal of identified publications revealed that the quality of economic evaluations varied widely from 42 to 87% of maximum score. It is very much in line with other studies. For example, the quality score of economic analysis of breast cancer control was in a similar range, i.e. from 23% to 86% [6].

First, the costs data needs to be carefully researched and presented. The domain of 'cost estimation' was appraised with the lowest score across included studies. The breakdown of costs into the rates of healthcare resources utilization and unit costs was missed as well as the details of the data source used for the cost estimation. Finally, the societal perspective was not adopted either. Following Edmunds (2018) it has to be underlined that the lack of costing data might cause under or overestimation of the impact of a given program, but also the robustness of economic analysis [27]. It does limit the opportunity to compare the costs of given procedure across different settings as well. The potential explanation of the lack of breakdown into unit costs and resource use can be found in the structure of the reimbursement system of hospital services which principles do not require such level of details. On that note, the contextualization for cost effectiveness analysis is an important aspect to be considered for any cost estimations as well. Patterns in the use of medical devices might not be determined only by clinical indication and its technical capabilities but also by incentives built in healthcare financing models. The differences in reimbursement coverage of similar procedures across jurisdictions or type of care settings (hospital and ambulatory) might influence the real-life use of MDs and distort its costs assessment from a broader perspective. Additionally, it must be mentioned that the inclusion of the indirect costs was missing across all included studies. It is a surprising finding if one considers the fact how much the caregiver burden limb ischemia may cause. The problem of the lack of the adoption of the societal perspective in the economic evaluation of medical devices should be seen from a much broader perspective. The implementation of MDs in clinical practice produces the impact beyond clinical outcome. Broader societal perspective is preferable as it can include intersectional outcomes, which later produce a comprehensive economic evaluation. The innovation may lead to faster recovery and increase patient's productivity to the society. Still, the understanding how to quantify for indirect costs seems to be missing among some experts working on cost effectiveness of medical devices. For example Vaidya's study (2014), although it adopted a societal perspective, failed to address certain cost items [28].

Second, while the utilization of local real-world data needs to be further enhanced, the limitation of CEA results' transferability has to be acknowledged. Several Authors highlighted the limitation related to generalizability of study findings [14,15,18,19,20]. In contrast to pharmaceuticals, the understanding of MDs' value will certainly require more insights into its real-life use, which however limits the CEA's applicability only to given local settings. On that note, it must be mentioned that out of 18 publications, there were only six studies that used RCTs data. Generally speaking, RCTs are difficult to conduct due to medical device characteristics [29,30,31]. Despite some already recognized aspects such as learning curve of end users, difficulties to blind patients, there are other arguments in favor of real-life local observational studies instead of RCTs. In many instances the choice of medical device for certain indications is done solely by a healthcare professional at his own discretion depending the patient's characteristics and his personal preferences. As a result, the study of specific health conditions may be unique in each setting given the availability of various alternative treatment options, along with adjunctive therapies. The current review revealed that as many as 10 out of 18 studies were using more than one comparison in their cost effectiveness analysis. The greater the reliance on Real World Data (RWD), the greater the issues of context dependence and patient heterogeneity. The generalizability of findings of any economic evaluation requires extra caution. Therefore, future CEA should rely more on local data but consequently confront the issues of findings' generalizability. There is a high likelihood of variety of CEA results driven not by technical success of MD but differences in local clinical practice such as healthcare professionals' preferences towards choices of indications for use and the availability of alternative treatment options.

Third, the choice of time horizon should be sufficient to fully account for the consequences of a given treatment [13]. However, the majority of reviewed studies used short follow-ups. It actually ranged from one year to 100 years [19,23,9]. Some experts, for example Vaidya (2014), argued against the use of brief-time horizons. Being not consistent with the chronic nature of assessed diseases such approach fails to assess the impact of therapeutic intervention in the long term correctly [28]. An adequate time horizon is required to capture all costs and consequences of a disease [32]. It questions the choice of health outcome, which may be different if longer time horizon is to be applied. Similar weaknesses are shown in the Edmunds study (2018); a short follow-up raised doubt whether the intervention would remain cost-effective in the long run [27]. The time of observation becomes more crucial for medical devices as they have unique characteristics compared to drugs: (1) a shorter life cycle; (2) the "learning curve" of healthcare professional with longer periods of observation yield higher efficacy of an MD; (3) price changes over time due to market dynamics [29,30,31]. In contrast to pharmaceuticals, the economic assessment of medical devices should therefore take into consideration multiple aspects related to the choice of time horizon. The future CEA for limb ischemia and generally medical devices should thus clearly adopt a sufficient follow-up that will allow specialists to observe the impact of treatment on relevant health outcomes. There is also a need to ensure appropriate model cycles adjusted to time need to observe changes in technical success rates along the learning curve of the end user.

Limitation

Our results should be considered with caution. First, the study was limited to 18 cost-effectiveness studies. Second, the adopted checklist for the critical appraisal was designed to assess general reporting and not preferable for both disease-specific model-based economic evaluation [33,34]. Still, it is hoped that our review can provide some contribution to the discussion about economic considerations regarding the treatment of critical limb ischemia.

Conclusions

In summary, it can be highlighted that the future economic studies of new treatment modalities for critical limb ischemia should focus more on the greater transparency and robustness in the presentation of costs. Specifically, the impact of different reimbursement mechanisms on the real use of given MD and consequently its value assessment needs to be accounted for too. The future economic studies should address the challenge of limited availability of RCTs as well. In the absence of such data, greater reliance on local data collection for the economic assessment has to be considered. Finally, specific attention regarding appropriate time horizon is required, too. The follow-up needs to be long enough to account for the impact of treatment on the meaningful health outcome while taking into consideration disease characteristics, along with healthcare professionals' preferences and the availability of different treatment modalities.

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