Angiosome-directed revascularization in patients with critical limb ischemia.

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ABSTRACT

Objective

Direct revascularization (DR), according to the angiosome concept, provides direct blood flow to the site of tissue loss in patients with critical limb ischemia (CLI). DR may lead to improved outcomes; however, evidence for this is controversial. This systematic review and meta-analysis investigates the outcomes of surgical and endovascular DR compared with indirect revascularization (IR) in patients with CLI.

Methods

A systematic review was undertaken using the Cochrane Collaboration specified tool. Additionally, a meta-analysis was done according to the MOOSE (Meta-analysis of Observational Studies in Epidemiology) criteria. The electronic databases of MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched for studies comparing DR vs IR in patients with CLI with tissue loss. All articles were critically assessed for relevance, validity, and availability of data regarding patient and lesion characteristics and outcomes. When possible, data were systematically pooled, and meta-analysis was performed for wound healing, major amputation, amputation-free survival, and overall survival.

Results

Of 306 screened abstracts, 19 cohort studies with 3932 patients were included. Nine scored 7 or higher on the Newcastle-Ottawa score. DR significantly improved wound healing (risk ratio [RR], 0.60; 95% confidence interval [CI], 0.51-0.71), major amputation (RR, 0.56; 95% CI, 0.47-0.67), and amputation-free survival rates (RR, 0.83; 95% CI, 0.69-1.00) compared with IR. This significance was lost in major amputation on sensitivity analysis for bypass studies. There was no significant difference in overall survival. In studies stratifying for collaterals, no differences between DR and IR were found in wound healing or major amputations in the presence of collaterals.

Conclusions

DR significantly improves wound healing and major amputation rates after endovascular treatment in patients with CLI, supporting the angiosome theory. In the presence of collaterals, outcomes after IR are similar to outcomes after DR. Alternatively, patients without collaterals may benefit even more from DR as a primary treatment strategy. In bypass surgery the angiosome theory is less applicable, since bypasses are generally anastomosed to the least affected artery with run-off passing the ankle in order to maintain bypass patency.

INTRODUCTION

Critical limb ischemia (CLI) is the most advanced stage of peripheral arterial occlusive disease (PAOD). The prognosis is poor, with amputation rates up to 30% and mortality up to 25% after 1 year.[1] Treatment of CLI aims at wound healing, improvement in quality of life, limb loss prevention, and prolonged survival.[1,2] Current strategies propose open or endovascular revascularization of infrapopliteal arteries with runoff through the ankle, but not specifically targeted to the location of the ischemia.[3–5]

Taylor and Palmer[6] introduced the angiosome concept nearly 30 years ago to provide a basis for the logical planning of incisions and flaps. An angiosome is a three-dimensional unit of tissue fed by a source artery. There are six recognizable angiosomes considering the foot and ankle. Three angiosomes originate from the posterior tibial artery (medial calcaneal artery angiosome, medial plantar artery angiosome, lateral plantar artery angiosome), one from the anterior tibial artery (dorsalis pedis angiosome), and two from the peroneal artery (lateral calcaneal artery angiosome, anterior perforator artery angiosome). Although not originally ment for CLI, the angiosome concept is widely embraced by endovascular specialist in their treatment paradigm.

Angiosomes are connected with each other through collaterals that can compensate for ischemic events in adjacent angiosomes. However, even with sufficient tibial and pedal vascularization, healing failure rates and limb loss of ~15% have been described in patients with CLI.[7,8] Moreover, severe atherosclerosis of the foot arteries can affect compensatory mechanisms, especially in diabetic patients.[9,10]

Direct revascularization (DR) of the feeding artery of the affected angiosome is expected to improve wound healing and limb salvage compared with indirect revascularization (IR). Systematic reviews with meta-analysis of retrospective studies comparing DR and IR suggest that DR may improve wound healing and limb salvage rates.[11–13] Nevertheless, evidence is controversial[10,14–17] because IR may be sufficient when collaterals are present.[10,18,19] DR and IR of the tibial arteries have recently been compared in larger cohorts of patients with CLI. The objective of this study was to perform a systematic review with meta-analysis of the outcomes after both open and endovascular DR of infrapopliteal arteries compared with IR, in particular, with or without the presence of collaterals, in patients with CLI.

METHODS

Search strategy, data sources, and study selection

A systematic review was undertaken using the Cochrane Collaboration specified tool.[20] To ensure a high-quality review, all aspects of the checklist of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group were followed.[21] A formal review protocol was published at www.crd.york.ac.uk/PROSPERO with the registration number CRD42016037082

The electronic databases of MEDLINE, Embase, the Cochrane Library, and the Current Controlled Trials register were searched. The last search was conducted on April 15, 2016. There were no limitations on publication date. Only English publications were included.

The free text word "angioso*" was used and included angiosoma, angiosomal, angiosome, angiosomes, angiosomic, angiosonics, angiosonographic, angiosonography, and angiosonoplasty. References and bibliographies of relevant papers were searched for additional references.

Studies were included if they met the following criteria:

1. Participants: patients with CLI.
2. Intervention: DR was described as an intervention on the infrapopliteal artery directly in line with the affected angiosome vs IR. IR can be subdivided as with or without the presence of collaterals. Open and endovascular techniques were both allowed.
3. Outcome measures: wound healing, major amputation, amputation-free survival, and death.
4. Types of study: randomized controlled trial and observational. Only full-text articles were assessed. No conference abstracts were included.

Data extraction, outcome measures, and assessment of study quality

Studies were evaluated for inclusion independently by two investigators (H.J. and J.B.) based on title and abstract and finally evaluated independently based on the full text. Disagreements were resolved by a third investigator (B.F.). Two investigators (H.J. and J.B.) independently extracted data from the eligible studies and entered the data on a standardized data form. Data were only retrieved from the articles. No attempt was made to obtain missing data from the authors. When available, propensity-matched data were used for meta-analysis.

Outcome variables were wound healing, defined as the percentage of patients with complete epithelialization of the target lesion with or without adjunct intervention (debridement, grafting, minor amputations, etc) at specified times during follow-up; major amputation, defined as the percentage of patients with an amputation above the ankle; amputation-free survival, defined as the percentage of patients alive without undergoing a major amputation; and survival, defined as the percentage of patients alive. Collaterals were an intact pedal arch or distal peroneal branches to the artery in the affected angiosome visible on angiography.

Because only observational studies were expected to be found, we used the Newcastle-Ottawa score to assess the quality of the studies.[22] This score assigns points for patient selection (maximum, 4 points), comparability of the cohort (maximum, 2 points), and outcome assessment (maximum, 3 points). Studies with a score of ≥7 were considered to be of higher quality.

Statistical analysis

Meta-analysis was performed when at least two studies existed with similar outcome, similar treatment, and control groups. Owing to expected clinical diversity of the included trials, a random-effects model, which accounts for the heterogeneity of studies through a statistical parameter representing the interstudy variation, was used to pool data and calculate the risk ratios (RRs) with 95% confidence intervals (CIs) to evaluate the statistical difference between outcomes after DR or IR. When available, data after 1 year were reported, if not available stated otherwise. Statistical heterogeneity was assessed for wound healing, major amputation, amputation-free survival, and mortality by calculating the I^2 statistic and Q statistic. Funnel plots were produced to assess publication bias. Sensitivity analysis on each outcome was performed for high-quality studies, endovascular treatment and bypass surgery. When available, subgroup analysis of IR with and without collaterals was performed. A two-sided P value of <.05 was considered statistically significant. Analyses were performed with Review Manager 5.3 software (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark).

RESULTS

Study selection

A total of 306 titles were screened for relevancy, and 19 articles were included in the outcome analysis.[10,15–17,23–37] A summary of the article selection process is depicted in Figure 1. The 19 articles included 3932 patients with treatment of 4097 limbs. Studies were prospective or retrospective cohort studies, and no randomized trials were identified (Table I).

Iida et al published three studies in 2010,[27] 2012,[26] and 2014.[28] All articles report endovascular treatment of a single below-the-knee vessel in patients from the Japan Below-the-Knee Artery Treatment (J-BEAT) registry. In the 2012 article (n = 329), Iida et al reported that 46 patients had already been included in the 2010 article (n = 177). The 2014 article (n = 529) did not state how many patients were included in the previous studies. The studies of Varela et al and Acin et al also shared a small portion of patients; however, the exact number is not mentioned.[10,23]

Study characteristics

All studies included patients with PAOD Rutherford classes 5 and 6. Three studies also included patients with PAOD Rutherford class 4; however, data from these patients were not used in the outcome analysis.[17,25,30] Six studies included only diabetic patients.[16,23,24,29,32,35]

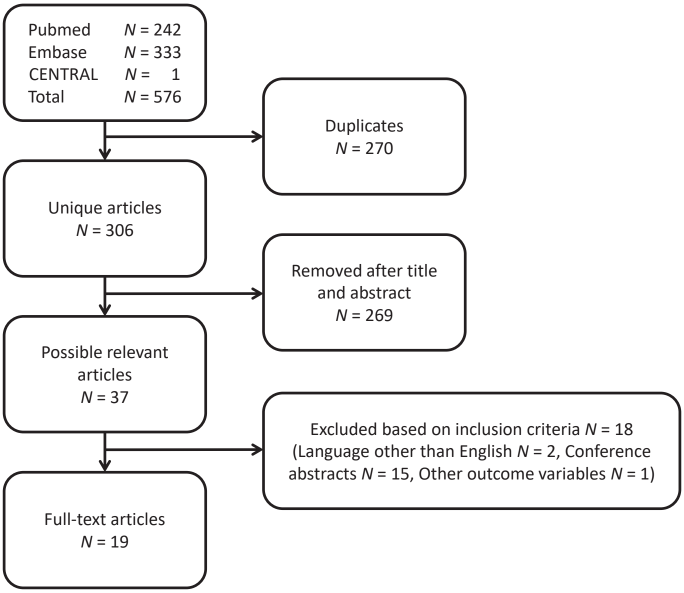


Figure 1. Study selection process

Five studies provided propensity-matched groups.[15,26,28,35,36] One study adjusted for runoff score in multivariate analysis to compare wound healing between the DR and IR group.[31] The type of surgery was endovascular in 12 studies,[16,23–29,34–37] bypass in 5,[15,17,31–33] and both endovascular and bypass surgery in 2.[10,30] Four of the five bypass surgery studies included only venous bypasses,[10,15,31,32] and three included venous and polytetrafluoroethylene bypasses.[17,30,33] The total number of patients with surgical bypass was 664 patients and the number of patients with endovascular treatment was 3265. Three patients received hybrid procedure.

The revascularization protocol was angiosome-directed in seven studies. This means that DR was primarily attempted, and if DR could not be obtained, IR was performed.[16,17,26–29,32]; In three studies, the least disease-affected artery in which uninterrupted flow passing the ankle could be obtained was revascularized.[15,25,31] One study divided patients before and after 2005 when the revascularization protocol switched from the least disease-affected artery to angiosome-directed revascularization.[24] Eight studies did not report their revascularization protocol. In these studies the authors scored in retrospect whether DR or IR was performed.[10,23,30,33–37]

Nine studies reported dual-antiplatelet therapy as postoperative medication after endovascular treatment,[16,24–26,28–30,35,37] whereas dual-antiplatelet therapy[17] or oral anticoagulantion[30] was implemented after bypass surgery. Nine studies did not report the postoperative medication scheme.

Wound care consisted of preoperative or postoperative débridement of necrotic tissue combined with minor amputation, if necessary, in 15 studies.[10,15–17,23–26,28,30–33,35,37] Four studies did not specify the postoperative wound care.[27,29,34,36] Additional wound care consisted of negative pressure therapy in deep wounds in five studies,[10,15,17,35,37] application of recombinant fibroblast growth factor spray to the wounds to facilitate epithelization in a portion of the patients in three studies,[15,33,37] and split-skin grafting or free-flap transfer in some patients to treat large defects in three studies.[17,33,35] Study characteristics are presented in Table I. Demographics of included patients are reported in Table II.

Quality of studies

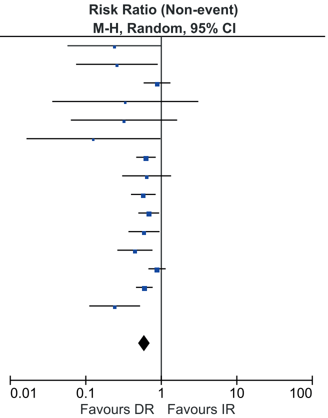
The Newcastle-Ottawa score was used to assess the quality of the studies, and nine were qualified as high-quality studies.[10,15–17,26,28,31,35–37] An overview of appointed scores can be found in Table III.

Wound healing

Wound healing was reported in 2683 patients in 15 studies.[10,15–17,23,24,28–31,33–37] Meta-analysis demonstrated a significantly better wound-healing rate after DR than after IR (RR by Mantel-Haenszel [$RR_{M\text{-}H}$], 0.60; 95% CI, 0.51-0.71; P < .001; Figure 2, Supplementary Figure 1, available online only). Heterogeneity was 39% among these studies (I^2 = 39%; χ^2 = 22.97; P = .006 for heterogeneity). Sensitivity analysis demonstrated significant improvement of wound healing rates after DR in high-quality studies, endovascular treatment and bypass procedures.

Study or Subgroup	DR Events	DR Total	IR Events	IR Total	Weight	Risk Ratio (Non-event) M-H, Random, 95% CI	Year
Neville 2009	20	22	13	21	1.3%	0.24 [0.06, 1.00]	2009
Varela 2010	42	45	23	31	1.7%	0.26 [0.07, 0.90]	2010
Alexandrescu 2011	98	134	68	98	9.4%	0.88 [0.58, 1.32]	2011
Azuma 2012	47	48	45	48	0.6%	0.33 [0.04, 3.09]	2012
Kabra 2013	37	39	21	25	1.1%	0.32 [0.06, 1.62]	2013
Osawa 2013	28	29	16	22	0.7%	0.13 [0.02, 0.98]	2013
Fossaceca 2013	87	151	11	34	12.6%	0.63 [0.47, 0.84]	2013
Rashid 2013	57	66	59	75	4.2%	0.64 [0.30, 1.35]	2013
Soderstrom 2013	58	84	39	84	10.2%	0.58 [0.40, 0.84]	2013
Iida 2014	137	182	116	182	11.9%	0.68 [0.50, 0.94]	2014
Acin 2014	30	46	16	39	7.9%	0.59 [0.37, 0.95]	2014
Kret 2014	41	54	24	52	6.8%	0.45 [0.26, 0.76]	2014
Spillerova 2015	180	252	170	252	13.6%	0.88 [0.67, 1.14]	2015
Zheng 2016	104	152	157	334	14.0%	0.60 [0.46, 0.77]	2016
Jeon 2016	55	63	9	19	3.9%	0.24 [0.11, 0.52]	2016
Total (95% CI)		**1367**		**1316**	**100.0%**	**0.60 [0.51, 0.71]**	
Total events	1021		787				

Heterogeneity: Tau² = 0.04; Chi² = 23.82, df = 14 (P = 0.05); I² = 41%
Test for overall effect: Z = 5.81 (P < 0.00001)



Figue 2. Wound healing.
The *solid squares* indicate the risk ratio and are proportional to the weights used in the meta-analysis. The *horizontal lines* represent the 95% confidence interval (*CI*). The *solid vertical line* indicates no effect. The *diamond* indicates the weighted mean difference and the lateral tips of the diamond indicate the associated CI. *DR*, Direct revascularization; *IR*, indirect revascularization; *M-H*, Mantel-Haenszel.

Table I. Study characteristics

Author	Study period	Type of study	Centers (no.)	Region	Patients (no.)	Limbs (no.)
Neville 2009[33]	A 2 year period before 2007	Retrospective	1	USA	48	52
Iida 2010[27]	April 2003 - August 2008	Retrospective	1	Japan	177	203
Varela 2010[10]	January 2005 - December 2008	Retrospective	1	Spain	70	76
Alexandrescu 2011[24]	September 2001 - April 2010	Retrospective	1	Belgium	208	232
Azuma 2012[15]	January 2003 - December 2009	Retrospective	1	Japan	228	249
Iida 2012[26]	April 2004 - October 2010	Retrospective	7	Japan	329	369
Fossaceca 2013[16]	January 2005 - December 2011	Retrospective	1	Italy	201	201
Kabra 2013[30]	January 2007 - September 2008	Prospective	1	India	64	64
Osawa 2013[34]	January 2005 - December 2009	Retrospective	1	Japan	51	51
Rashid 2013[17]	January 2004 - December 2011	Retrospective	1	England	154	141
Soderstrom 2013[35]	January 2007 - January 2011	Retrospective	1	Finland	226	250
Acin 2014[23]	January 1999 - December 2009	Retrospective	1	Spain	85	85
Iida 2014[28]	April 2004 - December 2012	Retrospective	11	Japan	539	539
Kret 2014[31]	January 2005 - December 2011	Retrospective	1	USA	106	106
Lejay 2014[32]	January 2003 - December 2009	Retrospective	1	France	54	58
Spillerova 2015[36]	January 2010 - July 2013	Retrospective	1	Finland	744	744
De athayde soares 2016[25]	January 2009 - January 2013	Retrospective	1	Brazil	92	109
Jeon 2016[29]	January 2011 - December 2013	Retrospective	3	Korea	70	82
Zheng 2016[37]	January 2005 - December 2014	Retrospective	1	China	486	486

n/s = not stated

[a] Multivariate analysis was used to compare wound healing between DR and IR groups while controlling for runoff score.

[b] Angiosome-directed = Direct revascularization (DR) according to the angiosome concept was attempted, if not possible or in case of failure indirect revascularization was attempted (IR); Least disease-affected = the least disease affected artery in which uninterupted run-off past the ankle could be obtained was revascularized

[c] A = Wound healing; B = Wound healing time; C= Major amputation; D = Amputation free survival; E = survival

Analysis method	Treatment modality	Revascularization protocol[b]	Specification of collaterals	Mean or median follow up	Endpoints [c]
				Months (± SD or range)	(Time of measurement in months)
Univariate analysis	Bypass surgery	n/s	No	n/s	A (n/s); B; C (n/s); E (n/s)
Univariate analysis	Endovascular	Angiosome-directed	No	n/s	C (12, 24, 36, 48)
Univariate analysis	Both	n/s	Yes	Median 14.3 (5.8-27.6)	A (12); B; C (24); E (12)
Univariate analysis	Endovascular	Before 2005 least-disease affected / After 2005 angiosome-directed	No	Mean 38.6 (1-68)	A (n/s); C (12, 24, 36); E (12, 24, 36)
Propensity matched	Bypass surgery	Least disease-affected	No	n/s, at least 1 year	A (12); C (24)
Propensity matched	Endovascular	Angiosome-directed	No	Mean 18 ± 16	C (12, 48); D (12, 48)
Univariate analysis	Endovascular	Angiosome-directed	No	Median 17.5 ± 12	A (12); C (12)
Univariate analysis	Both	n/s	No	n/s	A (6); C (6); E (6)
Univariate analysis	Endovascular	n/s	No	n/s	A (n/s); C (n/s)
Univariate analysis	Bypass surgery	Angiosome-directed	No	n/s	A (12); C (12)
Propensity matched	Endovascular	n/s	No	n/s	A (12); B; C (12); D (12); E (12)
Univariate analysis	Endovascular	n/s	Yes	Median 19 (9-38)	A (12); C (24); D (24); E (24)
Propensity matched	Endovascular	Angiosome-directed	No	Mean 21.6	A (12); B; C (12); D (24)
Multivariate analysis[a]	Bypass surgery	Least disease-affected	No	n/s	A (n/s); B; C (n/s)
Univariate analysis	Bypass surgery	Angiosome-directed	No	Mean 20 ±16	B; C (12, 36, 60); E (12, 36, 50)
Propensity matched	Endovascular	n/s	No	n/s	A (12); C (12, 24, 36, 48); D/E (12, 24, 36, 48)
Univariate analysis	Endovascular	Least disease-affected	No	Mean 14.3 ± 12.6	A (12); C (12); E (12)
Univariate analysis	Endovascular	Angiosome-directed	No	Mean 13 (0-25)	A (12); C (12)
Univariate analysis	Endovascular	n/s	Yes	n/s	A (12); C (12)

Table II. Demographics

Author	Mean age	Male	Diabetes	ESRD	Coronary disease
	(year)	(%)	(%)	(%)	(%)
Neville 2009	n/a	53.6%	87.5%	51.8%[a]	28.6%
Iida 2010	70.0	72%	68%	51%	54%
Varela 2010	octogenerians: 26.3%	57.9%	80.2%	3.9%	28.9%
Alexandrescu 2011	74.3	70.7%	100%	18%	85%
Azuma 2012	67.0	72%	81%	49%	54%
Iida 2012	69.0	68%	73%	63%	58%
Fossaceca 2013	75.5	67.1%	100%	7.4%	32.3%
Kabra 2013	n/a	82.8%	81.3%	n/a	31.2%
Osawa 2013	70.5	61.3%	77.5%	42.3%	n/a
Rashid 2013	75.0	75%	76%	28% [a]	44%
Soderstrom 2013	71.2	64%	100%	16%	64%
Acin 2014	72.0	61.4%	100%	0%	29.7%
Iida 2014	72.0	68.1%	68.9%	67.3%[a]	not stated
Kret 2014	67.8	70%	63%	12%	47%
Lejay 2014	69.5	68.5%	100%	54%	54%
Spillerova 2015	74.7	62%	61.3%	4.2%	37.4%
De athayde soares 2016	72.9	54.3%	76.1%	22.8%[a]	45.7%
Jeon 2016	69.6	72.8%	100%	34.2%	44.3%
Zheng 2016	69.1	83.8%	50%	n/a	18.9%

DR, Direct revascularization; *IR*, Indirect revascularization; *UTWCS*, University of Texas Wound Classification.
[a]Chronic renal disease
[b]Different stages of perceived peripheral neuropathie (UK screening test scale)

Hypertension	Smoker	Presence of neuropathy	Presence of infection	Rutherford classification, 5/6	Severity of wound
(%)	(%)			(%)	
39.3%	35.7%	n/a	n/a	n/a	n/a
82%	31%	n/a	n/a	71/29	n/a
72.4%	n/a	n/a	52.6%	n/a	deep lesion: 50%
86%	47%	84% [b]	69% > cellulitis 2cm	n/a	Wagner 1: 36%, Wagner 2: 64%, UTWCS-scale:1B-D 82 (35%) 2B-D 102 (44%) 3B-D 48 (21%)
65%	n/a	n/a	n/a	62/38	n/a
78%	27%	n/a	n/a	73/27	n/a
61.7%	n/a	n/a	n/a	n/a	n/a
59.4%	n/a	n/a	n/a	84/14	n/a
n/a	n/a	n/a	n/a	n/a	n/a
82.6%	61.7%	n/a	n/a	54/30	Wagner 2: 36.8% Wagner 3: 29.4% Wagner 4: 30.2% Wagner 5: 7.4%
75%	21%	n/a	39% (UTWCS D: 39%)	n/a	UTWCS 3: 55%
72.3%	74.3%	n/a	36.6%		n/a
72.4%	32.8%	n/a	n/a	72/28	n/a
77%	24%	n/a	60%	n/a	n/a
95.5%	71.5%	n/a	69.5%	n/a	Diabetic foot Armstrong classification; DR/1:27.7% 2:13.9% 3:52.8% 4:5.6% IR/ 1:27.5%, 2:29.3%, 3: 37.9%, 4: 5.2%
65.1%	14.3%	n/a	n/a	74/26	n/a
87%	n/a	n/a	83.7%	62/34	n/a
90%	n/a	n/a	n/a	n/a	Wagner 1-3: 35.4% Wagner 4-5: 64.6%
n/a	67.1%	n/a	42.5%	67/33	n/a

Table III. Newcastle-Ottawa Score

	Selection (max. 1 point per item)				Comparibility (max. 2 points)	Outcomes (max. 1 point per item)			
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Total**
Neville 2009	1	1	1	1	0	1	1	0	6
Iida 2010	1	1	1	1	0	1	1	0	6
Varela 2010	1	1	1	1	0	1	1	1	7
Alexandrescu 2011	1	0	1	1	0	1	1	0	5
Azuma 2012	1	1	1	1	2	1	1	1	9
Iida 2012	1	1	1	1	2	1	1	0	8
Fossaceca 2013	1	1	1	1	0	1	1	1	7
Kabra 2013	1	1	1	1	0	1	0	1	6
Osawa 2013	1	1	1	1	0	1	0	1	6
Rashid 2013	1	1	1	1	0	1	1	1	7
Soderstrom 2013	1	1	1	1	2	1	1	0	8
Acin 2014	1	1	1	1	0	1	1	0	6
Iida 2014	1	1	1	1	2	1	1	0	8
Kret 2014	1	1	1	1	1	1	1	0	7
Lejay 2014	1	1	1	1	0	1	1	0	6
Spillerova 2015	1	1	1	1	2	1	1	0	8
De athayde soares 2016	1	1	1	1	0	1	1	0	6
Jeon 2016	1	1	1	1	0	1	1	0	6
Zheng 2016	1	1	1	1	0	1	1	1	7

Per question 1 point could be awarded (with the exception of comparibility where 2 points could be awarded). Points were awarded if:

1. Representativeness of the exposed cohort; Patients with critical limb ischemia undergoing endovascular or surgical infrapopliteal intervention

2. Selection of the non exposed cohort; Patients were drawn from the same community as the exposed cohort

3. Ascertainment of exposure; Data was obtained from secure records

4. Demonstration that outcome of interest was not present at start of study

5. Comparability of cohorts on the basis of the design or analysis; 1 point if matched by study design, 1 point if adjusted for confounders

6. Assessment of outcome; Outcomes were assessed from indepent blind assessment or record linkage

7. Follow-up was long enough for outcomes to occur; follow up at least 1 year

8. Adequacy of follow up of cohorts; <10% of cohort lost to follow up

Time to wound healing

Six studies reported time to wound healing in the DR group compared with the IR group.[10,28,31–33,35] Pooling the data was not possible, because these were too heterogeneous in format to combine. All studies, except one,[33] found a shorter healing time in the DR group than in the IR group. This difference was statistically significant in three studies.[31,32,35]

Major amputation

Data on major amputation were available in all studies. Results from one study could not be used because the definition of amputation was not clear.[32] Meta-analysis was performed on 3230 patients. A significant reduction of major amputation was found after DR compared with IR ($RR_{M\text{-}H}$, 0.56; 95% CI, 0.47-0.67; P < .001; Figure 3, Supplementary Figure 2, available online only). Heterogeneity among the studies was low (I^2 = 0%, χ^2 = 14.69, P = .58 for heterogeneity). Sensitivity analysis demonstrated a significant reduction of major amputation after DR in high-quality studies and endovascular treatment, compared with IR. No significant reduction was found after DR in bypass studies (Table IV).

	DR		IR			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Neville 2009	2	22	8	21	1.5%	0.24 [0.06, 1.00]	2009
Varela 2010	3	45	9	31	2.1%	0.23 [0.07, 0.78]	2010
Iida 2010	17	118	26	85	10.5%	0.47 [0.27, 0.81]	2010
Alexandrescu 2011	13	134	16	98	6.6%	0.59 [0.30, 1.18]	2011
Iida 2012	18	118	31	118	11.4%	0.58 [0.34, 0.98]	2012
Azuma 2012	1	48	4	48	0.7%	0.25 [0.03, 2.16]	2012
Fossaceca 2013	16	167	3	34	2.2%	1.09 [0.33, 3.52]	2013
Osawa 2013	1	29	6	22	0.7%	0.13 [0.02, 0.98]	2013
Rashid 2013	1	66	3	75	0.6%	0.38 [0.04, 3.55]	2013
Soderstrom 2013	12	84	19	84	7.2%	0.63 [0.33, 1.22]	2013
Kabra 2013	6	39	6	25	3.0%	0.64 [0.23, 1.77]	2013
Acin 2014	5	46	14	39	3.6%	0.30 [0.12, 0.77]	2014
Iida 2014	15	182	25	182	8.4%	0.60 [0.33, 1.10]	2014
Kret 2014	6	54	6	52	2.7%	0.96 [0.33, 2.80]	2014
Spillerova 2015	40	252	64	252	24.7%	0.63 [0.44, 0.89]	2015
Zheng 2016	16	152	68	334	11.9%	0.52 [0.31, 0.86]	2016
Jeon 2016	2	63	0	19	0.3%	1.56 [0.08, 31.21]	2016
de Athayde Soares 2016	6	48	3	44	1.8%	1.83 [0.49, 6.89]	2016
Total (95% CI)		**1667**		**1563**	**100.0%**	**0.56 [0.47, 0.67]**	
Total events	180		311				

Heterogeneity: Tau² = 0.00; Chi² = 14.69, df = 17 (P = 0.62); I² = 0%
Test for overall effect: Z = 6.37 (P < 0.00001)

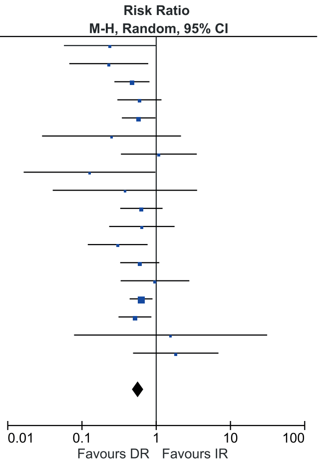


Figure 3. Major amputation.
The *solid squares* indicate the risk ratio and are proportional to the weights used in the meta-analysis. The *horizontal lines* represent the 95% confidence interval (*CI*). The *solid vertical line* indicates no effect. The *diamond* indicates the weighted mean difference and the lateral tips of the diamond indicate the associated CI. *DR*, Direct revascularization; *IR*, indirect revascularization; *M-H*, Mantel-Haenszel.

Amputation-free survival

Five studies reported amputation-free survival in 1357 patients after 1 year[26,35,36] or 2 years.[23,28] When pooled, a significant improvement after DR was found compared with IR (RR_{M-H}, 0.83; 95% CI, 0.69-1.00; P = .04). Heterogeneity among the studies was low (I^2 = 36%, χ^2 = 6.21, P = .18 for heterogeneity). No sensitivity analysis was performed because of the low number of studies with available data.

Survival

Survival rates were reported in 16 studies.[10,15–17,23–26,29,30,32–37] In seven, only the survival rate for the whole cohort was reported.[15–17,26,29,34,37] Data from nine studies could be pooled, and meta-analysis was performed on 1348 patients. No significant difference was found after DR compared with IR (RR_{M-H}, 0.92; 95% CI, 0.75-1.14; P = .46; Figure 4, Supplementary Figure 3, available online only). Heterogeneity among the studies was low (I^2 = 0%, χ^2 = 6.09, P = .64 for heterogeneity). No significant differences were found after sensitivity analysis (Table IV).

Study or Subgroup	DR Events	DR Total	IR Events	IR Total	Weight	Risk Ratio (Non-event) M-H, Random, 95% CI	Year
Neville 2009	22	27	21	25	3.1%	1.16 [0.35, 3.83]	2009
Varela 2010	39	45	23	31	4.8%	0.52 [0.20, 1.34]	2010
Alexandrescu 2011	125	134	88	98	5.9%	0.66 [0.28, 1.56]	2011
Soderstrom 2013	62	84	62	84	17.0%	1.00 [0.60, 1.66]	2013
Kabra 2013	35	39	19	25	3.2%	0.43 [0.13, 1.36]	2013
Acin 2014	28	36	14	22	6.4%	0.61 [0.27, 1.39]	2014
Lejay 2014	34	46	31	39	7.1%	1.27 [0.58, 2.79]	2014
Spillerova 2015	192	252	194	252	43.8%	1.03 [0.75, 1.42]	2015
de Athayde Soares 2016	46	59	39	50	8.7%	1.00 [0.49, 2.04]	2016
Total (95% CI)		**722**		**626**	**100.0%**	**0.92 [0.75, 1.14]**	
Total events	583		491				

Heterogeneity: Tau² = 0.00; Chi² = 6.09, df = 8 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)

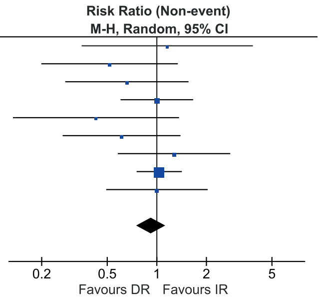


Figure 4. Survival.
The *solid squares* indicate the risk ratio and are proportional to the weights used in the meta-analysis. The *horizontal lines* represent the 95% confidence interval (*CI*). The *solid vertical line* indicates no effect. The *diamond* indicates the weighted mean difference and the lateral tips of the diamond indicate the associated CI. *DR*, Direct revascularization; *IR*, indirect revascularization; *M-H*, Mantel-Haenszel.

Presence of collaterals

Three studies comprising 641 patients divided the IR group by those with and without collaterals.[10,23,37] Significant improvement of wound healing (RR_{M-H}, 0.37; 95% CI, 0.30-0.46; P < .001) and major amputation rates (RR_{M-H}, 0.28; 95% CI, 0.16-0.47; P < .001) were found after DR compared with IR without collaterals. Compared with IR with collaterals, no significant improvements were found for wound healing (RR_{M-H}, 0.90; 95% CI, 0.69-1.19; P = .47) or major amputation (RR_{M-H}, 0.71; 95% CI, 0.42-1.17; P = .18). No significant differences were found in survival rates after DR and IR, with and without collaterals (Figure 5).

Table IV. Sensitivity analysis for wound healing, major amputation and survival

Sensivity analysis	No of studies	DR	IR	Heterogeneity I^2	Chi^2	Heterogeneity P	RR (95% CI)	Overal effect of Z	P-value
	n. (limbs)	(n)	(n)	(%)			Mantel-Haenszel [RR_{M-H}]		
Wound healing									
All	15 (2683)	1367	1316	39	22.97	.06	0.60 [0.51-0.71]	5.89	<.00001
High quality studies (NO-score ≥ 7)	9 (2126)	1034	1092	15	9.42	.31	0.65 [0.56, 0.74]	6.03	<.00001
Endovascular	9 (2157)	1093	1064	52	16.81	.03	0.64 [0.53, 0.77]	4.64	<.00001
Bypass	4 (386)	190	196	0	1.64	.65	0.47 [0.31, 0.71]	3.63	.0003
Major amputation									
All	18 (3230)	1667	1563	0	14.69	.62	0.56 [0.47, 0.67]	6.37	<.00001
High quality studies (NO-score ≥ 7)	9 (2142)	1050	1092	0	5.30	.72	0.59 [0.47, 0.74]	4.52	<.00001
Endovascular	12 (2704)	1393	1311	0	9.45	.58	0.58 [0.48, 0.70]	5.77	<.00001
Bypass	4 (386)	190	196	0	2.97	.40	0.50 [0.24, 1.06]	1.80	.07
Survival									
All	9 (3535)	722	626	0	6.09	.64	0.92 [0.75, 1.14]	0.74	.46
High quality studies (NO-score ≥ 7)	3 (748)	381	367	0	1.85	.40	0.97 [0.75, 1.26]	0.19	.85
Endovascular	5 (1098)	575	523	0	1.30	.86	1.01 [0.80, 1.27]	0.08	.94
Bypass	2 (110)	63	47	0	0.75	.39	0.75 [0.38, 1.48]	0.83	.41

DR, Direct revascularization; *IR*, indirect revascularization; *NO-score*, Newcastle-Ottawa score.

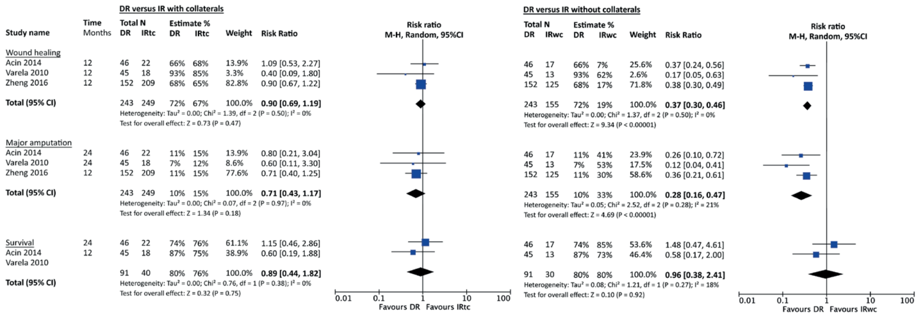


Figure 5.

Indirect revascularization (*IR*) with and without collaterals. The *solid squares* indicate the risk ratio and are proportional to the weights used in the meta-analysis. The *horizontal lines* represent the 95% confidence interval (*CI*). The *solid vertical line* indicates no effect. The *diamond* indicates the weighted mean difference and the lateral tips of the diamond indicate the associated CI. *DR*, Direct revascularization; *M-H*, Mantel-Haenszel.

DISCUSSION

This systematic review with meta-analyses of >4000 limbs in patients with CLI represents the largest collected study comparing DR and IR of the infrapopliteal arteries with regard to the angiosome concept. Overall, DR demonstrated significant improvement of wound healing, major amputation, and amputation-free survival rates compared with IR. Survival rates were comparable after DR and IR. A small portion of the studies differentiated IR by the presence of collaterals. These data suggest that the collaterals strongly influence wound healing and major amputation rates.

Compensatory mechanisms

Compromised vascularization to the foot can be compensated by direct arterial connections, such as collaterals and the pedal arch, and indirect connections, known as choke vessels.

In our review, we were able to pool data from three studies differentiating outcomes after IR with and without collaterals (an intact pedal arch or distal peroneal branches to the artery in the affected angiosome visible on angiography).[10,23,37] These studies suggest that in the presence of collaterals, outcomes after IR may be similar to outcomes after DR. Alternatively, patients without collaterals may benefit even more from DR as a primary treatment strategy.

Besides visible collaterals, there is a network of reduced-caliber choke vessels that mark the outer lining of the angiosome. These vessels are not capable of perfusing the adjacent angiosome; however, when a particular angiosome becomes compromised, the choke vessels open to improve vascularization of the adjacent angiosome.[38] The compensatory system provided by this network in nonatherosclerotic and nondiabetic patients might be damaged in patients with miscellaneous systemic arterial disease.[18,39]

Rashid et al[17] and Kret et al[31] evaluated the effects of the presence of a pedal arch. Rashid et al[17] found that the quality of the pedal arch did not influence rates of patency or amputation-free survival in patients undergoing infrapopliteal bypass for CLI. However, the healing rate and time to healing were directly influenced by the quality of the pedal arch rather than the angiosome revascularized.[17] Kret et al[31] concluded that improvements in wound healing in the DR group might be attributed to the target vessel itself (ie, DR vs IR) rather than to the presence of a network of collateral vessels.

Revascularizing more than one artery seems an attractive option in endovascular procedures to ensure sufficient blood flow to the foot and the affected angiosomes. However, both Acin et al[23] and Jeon et al[29] found no significant improvement in wound healing and amputation rates when more than one vessel was revascularized. This observation was confirmed in a study by de Athayde Soares et al.[40] dedicated to this subject.

The role of revascularization protocol

Several revascularization protocols were implemented among the included studies. Roughly, these can be divided as angiosome-directed and treatment of the least disease-affected artery. In a portion of the studies the protocol was not stated. In angiosome-directed studies, DR is attempted with respect to the angiosome concept and if failed or not possible, IR was performed. In the least disease-affected artery treatment protocols the least disease-affected artery is chosen, which may be either DR or IR. Only two of the seven bypass surgery studies implemented an angiosome-directed revascularization protocol. Bypasses are generally anastomosed distally to the least affected artery with run-off passing the ankle because the quality of the outflow artery is a more important determinant of patency than the actual level of the distal anastomosis.[1] This is probably the reason for the low number of bypass studies implementing an angiosome-directed revascularization protocol. Angiosome-directed revascularization seems less important in bypass surgery, because no significant improvement of major amputation rates was found after sensitivity analysis of bypass studies; however, numbers are small in the sensitivity analysis.

In endovascular treatment, as opposed to bypass surgery, attempting DR of severely affected arteries or occluded arteries is possible. Significant improvement after DR was observed for wound healing, major amputation, and amputation-free survival after sensitivity analyses of endovascular studies. This result suggests that, whenever possible, DR should be attempted in patients where endovascular treatment is indicated.

Contributing factors to wound healing

Restoring blood flow to the anatomical location of the wound is a main contributing factor of wound healing.[41] However, anatomical location and extent of the tissue loss,[41,42] as well as systemic factors, are associated with delayed wound healing.[41,43,44] Multivariate analysis in the study of Azuma et al[15] marked end-stage renal disease, diabetes, low albuminemia, and Rutherford-Baker classification 6 as predicting factors for clinical failure after bypass surgery. Data on lesion characteristics in this review were limited. In only five studies was a wound classification score reported.[17,24,29,32,35] Furthermore, comprehensive data on wound size were lacking. This is considered a limitation of this review, because ulcer size >5 cm indicates a reduced chance of healing and an increased risk of major amputation.[45] The differences in postoperative wound care regimens that existed among the trials should also be considered a limitation, because adequate postoperative wound care improves wound-healing rates.[44,46]

Clinical end points and new techniques

Clinical end points assessing preoperative and postoperative outcomes in this study were wound healing and major amputation, which are relevant outcome parameters in patients with advanced disease (Rutherford 5 and 6). In patients with intermittent claudication or rest pain, the angiosome model cannot be implemented as easily because pain is not specifically related to an angiosome. New techniques, such as perfusion angiography, indocyanine green angiography and measurement of transcutaneous pressure of oxygen, may contribute in future research to localize the focus of less perfused locations and observe changes in preoperative and postoperative perfusion.[47,48]

Limitations

Although almost half of the studies were qualified as high-quality studies according to the Newcastle-Ottawa score, almost all studies were retrospective case series. These studies are at risk for selection bias and must be interpreted with caution. Higher levels of evidence should be obtained with prospective and randomized controlled trials. Funnel plot asymmetry may indicate publication bias for wound healing (Supplemental Figure 1). There were differences in inclusion criteria, treatment strategies, and postoperative care regimens. Data on the severity of the tissue loss were not available in most studies. These differences and lack of data impede comparing groups. Only six of the 19 studies adjusted for differences after multivariate analysis[31] or implemented propensity matching.[15,26,28,35,36] Parts of the reported data in three studies were reported in earlier studies; however, these portions were small.[23,26,28] During the analysis, we experienced low statistical heterogeneity for major amputation and survival; however, a random-effects model was chosen beforehand owing to the clinical diversity of the included trails.

CONCLUSIONS

DR significantly improves wound healing and major amputation rates after endovascular treatment in patients with CLI, supporting the angiosome theory. In the presence of collaterals, outcomes after IR are similar to outcomes after DR. Alternatively, patients without collaterals may benefit even more from DR as a primary treatment strategy. In bypass surgery the angiosome theory is less applicable, since bypasses are generally anastomosed to the least affected artery with run-off passing the ankle in order to maintain bypass patency.

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