Angiosome-targeted Lower Limb Revascularization for Ischemic Foot Wounds: Systematic Review and Meta-analysis

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WHAT THIS PAPER ADDS

The efficacy of angiosome-targeted revascularization to achieve healing of ischemic tissue lesions of the foot and limb salvage is controversial. The results of this meta-analysis suggest that, when feasible, direct revascularization of the foot angiosome affected may improve wound healing and limb salvage rates compared with indirect revascularization.

Objective: The efficacy of angiosome-targeted revascularization to achieve healing of ischemic tissue lesions of the foot and limb salvage is controversial. This issue has been investigated in this meta-analysis.

Methods: A systematic review of the literature and meta-analysis of data on angiosome-targeted lower limb revascularization for ischemic tissue lesions of the foot were performed.

Results: Nine studies reported on data of interest. No randomized controlled study was available. There were 715 legs treated by direct revascularization according to the angiosome principle and 575 legs treated by indirect revascularization. The prevalence of diabetes was >70% in each study group and three studies included only patients with diabetes. The risk of unhealed wound was significantly lower after direct revascularization (HR 0.64, 95% CI: 0.52—0.8, I^2 0%, four studies included) compared with indirect revascularization. Direct revascularization was also associated with significantly lower risk of major amputation (HR 0.44, 95% CI: 0.26—0.75, I^2 62%, eight studies included). Pooled limb salvage rates after direct and indirect revascularization were at 1 year 86.2% vs. 77.8% and at 2 years 84.9% vs. 70.1%, respectively. The analysis of three studies reporting only on patients with diabetes confirmed the benefit of direct revascularization in terms of limb salvage (HR 0.48, 95% CI: 0.31—0.75, I^2 0%).

Conclusions: The results of the present meta-analysis suggest that, when feasible, direct revascularization of the foot angiosome affected by ischemic tissue lesions may improve wound healing and limb salvage rates compared with indirect revascularization. Further studies of better quality and adjusted for differences between the study groups are needed to confirm the present findings.

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INTRODUCTION

Ischemic tissue lesions of the foot carry an excessive risk of major amputation, particularly in patients with diabetes.[1] Prompt referral of these patients to a vascular surgeon for assessment of lower limb circulation, revascularization, and surgical wound care may avoid limb loss.[2] A number of patients with infected wounds or gangrene of the foot still require major amputation despite an patent bypass graft or a successful angioplasty. Such failures to achieve limb salvage are often caused by aggressive infection or extensive gangrene of the ischemic foot. However, recent studies have suggested that the clinical success of bypass surgery or angioplasty may depend on the target of revascularization.[3] Two decades ago, Taylor and Palmer[4] recognized the clinical importance of angiosomes as three-dimensional units of tissues fed by a source artery. They defined six angiosomes of the foot and ankle originating from the posterior tibial artery (three angiosomes: the medial calcaneal artery angiosome, the medial plantar artery angiosome, and the lateral plantar artery angiosome), the anterior tibial artery (one angiosome: the anterior tibial artery and dorsalis pedis angiosome) and the peroneal artery (two angiosomes: the lateral calcaneal artery angiosome and anterior perforator artery angiosome). These angiosome units are bordered by choke vessels, which link neighbouring angiosomes to each other and demarcate the border of each angiosome.[5] Furthermore, direct arterial—arterial connections exist between angiosomes and compensate for ischemic events occurring in an adjacent angiosome. As compensatory

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collateral circulation can be affected by severe atherosclerosis of the foot arteries,[6] angiosome-targeted revascularization is expected to improve wound healing and limb salvage compared with indirect revascularization, which provides blood flow only through collateral vessels originating from a non-affected angiosome. In other words, direct revascularization of an artery feeding an area of the foot, the angiosome, affected by ischemic wound or gangrene is expected to have better chances of clinical success than revascularization of any other artery not directly feeding the affected anatomical area. However the results of angiosome-targeted revascularization are controversial.[6–10] In the present meta-analysis, the potential benefits of direct revascularization of ischemic tissue lesions of the foot has been investigated.

METHODS

A literature review was performed through PubMed, Scopus, Science Direct, and Google up to August 2013 for any study evaluating the outcome of lower limb revascularization according to the angiosome concept. Revascularization of an artery in line with the angiosome affected by a foot ischemic tissue lesion was defined as direct revascularization. The words employed in the search were: "angiosome", "limb", and "foot". Reference lists of obtained articles were also searched.

Inclusion criteria

Prospective and retrospective observational studies published in English, Spanish, or Italian reporting on the outcome of patients undergoing revascularization of the lower limb following (direct revascularization) or not (indirect revascularization) the angiosome principle were considered for this study. No date limit was set. Only studies reporting on comparative analysis of any surgical, endovascular, or hybrid direct versus indirect revascularization were considered for inclusion in the present analysis. As patients with critical limb ischemia are exposed to a high risk of random censoring mostly because of early and late mortality after revascularization, only studies reporting on actuarial data were included in this analysis.

Exclusion criteria

Data reported only in abstracts were not included in this analysis. Studies not reporting at least 6-month results were not included in this study. Data on mean or median time-to-event were not summarized because relevant times are only known for the subset of patients who had the event or were cured. This implies that censored patients must be excluded as otherwise this may be a source of bias.

Data collection and assessment of data quality

Articles potentially dealing with this topic were identified, data were abstracted independently by both investigators from all eligible studies using a standardized Excel file, data on study design, study size, patient demographics, types of intervention, and outcome were retrieved. Data were retrieved only from the articles and no attempt was made to get missing data from the authors. As only retrospective, observational studies were expected to be included in this analysis, the assessment of data quality was limited to verifying whether the study groups were adjusted for baseline variables or matched for any baseline variables or propensity score. The guidelines for Meta-analysis of Observational Studies in Epidemiology (MOOSE)[11] were applied.

Outcomes of interest

The main outcome end-points of this study were wound healing and limb salvage, which is freedom from major lower limb amputation. Secondary outcome end-points were survival and amputation-free survival.

Statistical analysis

Statistical analysis was performed using Review Manager 5.2 software (Version 5.2, The Nordic Cochrane Centre, Copenhagen, Denmark) and Open Meta-analyst (http://www.cebm.brown.edu/open_meta). The hazard ratios and standard errors were calculated from actuarial curves or data of individual studies using a graphical approach that showed time trends.[12] The natural logarithm of hazard ratio and its standard error of direct versus indirect revascularization were entered into Review Manager to estimate hazard ratios by generic inverse variance analysis. The pooled risk of adverse event was expressed as hazard ratio (HR) with 95% confidence interval (95% CI). Because heterogeneity was anticipated in these observational studies, this was taken into account *a priori* by using random effects models (DerSimonian—Laird). Heterogeneity across studies was evaluated using the I^2 test, assuming that $<40\%$ indicates a non-significant heterogeneity. This proportion meta-analysis was performed by estimating the ratio of the number of events and the number of legs at risk at 1- and 2-year intervals. Intermediate pooled overall leg salvage rates were estimated and plotted at 1- and 2-year study intervals, and hazard ratio was calculated using the graphical approach by Tierney et al.[12] A p value <0.05 was considered statistically significant.

RESULTS

A literature search was performed on August 19, 2013 and yielded 45 articles, of which nine[6–8,13–18] were found to report data of interest and fulfilled the inclusion criteria of the present study (Fig. 1). No randomized controlled study was available for this analysis.

Table 1 summarizes the main characteristics of these studies. These studies included 715 legs treated by direct revascularization and 575 legs treated by indirect revascularization. The studies reported a prevalence of diabetes $>70\%$ in each study group, and three studies[13,15,18] included only patients with diabetes. Only three studies[8,14,15] reported on propensity score matched analysis. Otherwise, none of these studies reported data

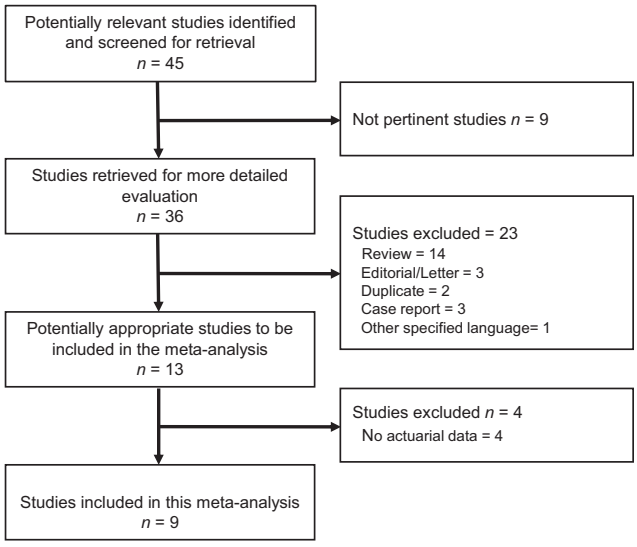


Figure 1. Literature search flow-chart.

adjusted for possible differences between the study groups.

Analysis of data from four studies reporting the wound healing rate[6,8,15,16] showed that the risk of unhealed wound was significantly lower after direct revascularization (HR 0.64, 95% CI: 0.52–0.8, I^2 0%, Figs. 2 and 3). Analysis of two studies[8,15] reporting data on propensity score matched analysis showed a trend toward a better wound healing rate after direct revascularization (HR 0.72, 95% CI: 0.50–1.04, I^2 29%). Analysis of data from eight studies reporting on limb salvage rates[6,7,13–18] showed that direct revascularization was associated with a significantly lower risk of major amputation compared with indirect revascularization (HR 0.44, 95% CI: 0.26–0.75, I^2 62%, Figs. 4 and 5). The analysis of three studies reporting only on diabetic patients[13,15,18] confirmed the benefit of direct revascularization in terms of limb salvage (HR 0.48, 95% CI: 0.31–0.75, I^2 0%). Exclusion of two studies with outlier HR (lnHR < -1.0)[17,18] confirmed the efficacy of direct revascularization in achieving limb salvage (HR 0.64, 95% CI 0.46–0.88, I^2 0%). Kabra et al.[16] included one patient with Rutherford class 4 in the direct revascularization group. When this study was excluded from the analyses, direct revascularization was still associated with significantly better wound healing (HR 0.65, 95% CI 0.53–0.80, I^2 0%) and limb salvage (HR 0.43, 95% CI 0.24–0.77, I^2 67%).

Fig. 6 summarizes the 2-year limb salvage rates after direct and indirect revascularization for ischemic tissue lesions of the foot. Pooled limb salvage rates after direct and indirect revascularization were 86.2% vs. 77.8% at 1 year and 84.9% vs. 70.1% at 2 years (six studies included).[6,7,13,14,18]

Only two studies[14,15] reported on amputation-free survival, showing only a trend in favour of direct revascularization over indirect revascularization (HR 0.81, 95% CI: 0.61–1.06, I^2 0%). Two studies[15,18] reported on similar survival in these two study groups (HR 0.79, 95% CI: 0.47–1.35, I^2 25%).

Table 1. Characteristics of observational studies evaluating the outcome after direct, angiosome-targeted revascularization versus indirect revascularization for ischemic tissue lesions of the foot.

Author	Year of publication	Type of study	Study period	Treatment method	Disease stage	No. limbs		Mean age (years)		Females (%)		Diabetes (%)		End-stage renal disease (%)		Coronary artery disease (%)		Follow-up (months)
						DR	IR	DR	IR	DR	IR	DR	IR	DR	IR	DR	IR	
Varela[6]	2010	R	2005–2008	Endo/Surg	ABI<0.50/TP < 50, wound	45	31	–	–	38	45	82	77	4	3	33	23	24
Alexandrescu[13]	2011	R	2001–2010	Endo	Diabetic ischemic wound	134	98	–	–	–	–	100	100	20	15	–	–	54
Blanes Orti[7]	2011	R	–	Endo	Rutherford 5–6	18	16	–	–	33	50	72	88	39	38	39	50	21
Azuma[8]	2012	R	2003–2009	Surg	Rutherford 5–6	126	92	67	68	25	26	80	80	53	45	–	–	24
Iida[14]	2012	R	2004–2010	Endo	AP<70/TP < 50, wound	173	153	70	70	28	35	71	76	50	56	50	56	48
Ferrufino-Mérida[17]	2012	P	2011–2012	Endo	CLI, wound	23	9	–	–	–	–	70	78	–	–	48	33	6
Söderström[15]	2013	R	2007–2011	Endo	Diabetic ischemic wound	121	129	68	74	26	45	100	100	21	10	57	54	12
Kabra[16]	2013	P	2007–2008	Endo/Surg	Rutherford 4–6[a]	39	25	–	–	18	16	77	88	–	–	18	52	6
Lejay[18]	2013	R	2003–2009	Surg	Diabetic ischemic wound	36	22	68	71	31	32	100	100	53	55	53	55	48

CLI = critical limb ischemia; DR = direct revascularization; IR = indirect revascularization; P = prospective study; R = retrospective study; Endo = endovascular; Surg = surgical; – = not reported; ABI = ankle brachial index; TP = toe pressure; AP = ankle pressure (pressure values are in mmHg).

[a] One patient with Rutherford stage 4 included in the direct revascularization group.

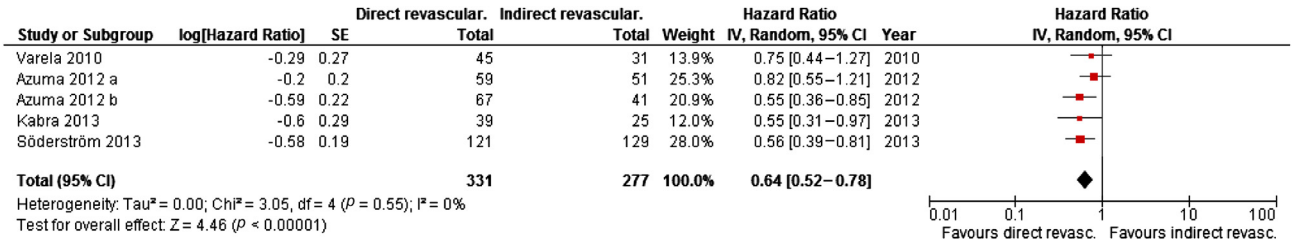


Figure 2. Forest plot for effectiveness of direct revascularization versus indirect revascularization according to the angiosome concept in wound healing in patients with ischemic tissue lesions of the foot.

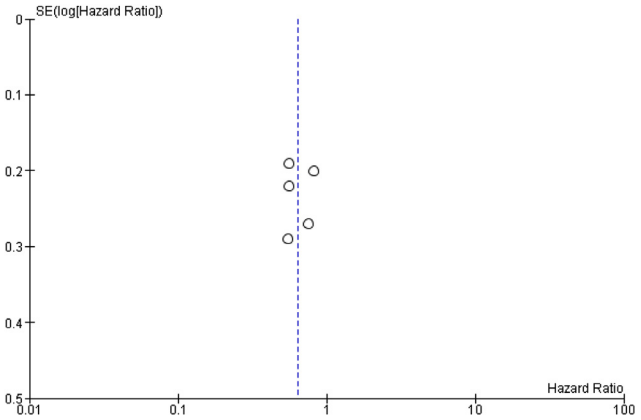


Figure 3. Funnel plot for effectiveness of direct revascularization versus indirect revascularization according to the angiosome concept in wound healing in patients with ischemic tissue lesions of the foot.

DISCUSSION

The present meta-analysis showed that direct revascularization of an artery feeding a foot angiosome affected by an ischemic tissue lesion may significantly improve the wound healing and limb salvage rates compared with indirect revascularization. These findings are of clinical relevance particularly because the significantly improved outcome after direct revascularization should be viewed in the light of current satisfactory limb salvage rates also achieved in the indirect revascularization group (Fig. 4). This means that achieving pulsatile arterial flow straight to the site of ischemic wound and gangrene is of critical importance to effectively treat wound infection, to accelerate the healing process and to avoid limb loss.

Although the efficacy of angiosome-targeted revascularization seems straightforward, a number of recent studies indicated its limited value.[7–10] However, the results of these studies might be affected by their small size,[6,7] by failing to consider censoring[9,10] or to adequately compare or report on the outcome after these two revascularization strategies.[8,9] Indeed, this meta-analysis showed a limited heterogeneity of the included studies and all of these showed a trend toward better wound healing and limb salvage rates. Pooled limb salvage rates indicate a marked advantage for direct revascularization over indirect revascularization in these high-risk patients (Fig. 4).

A number of limitations possibly affecting these results should be acknowledged. Seven out of nine studies were retrospective and this might introduce a significant bias, particularly in the assessment of the nature and severity of ischemic tissue lesions. Furthermore, patients included in the indirect revascularization group were possibly historical controls. The lack of comparability of the study groups was not properly addressed in these studies. In fact, only three studies adjusted for possible differences between the study groups by propensity score matching, but failed to report on all the main outcome end-points, thus preventing a through pooled analysis of their results. Furthermore, there are not enough data available to assess the comparability of the site, severity, duration, and methods of local treatment of these tissue lesions. In fact, only two large studies[13,15] stratified the severity of foot wound by using different wound classification systems and found a similar prevalence of severe wounds in the study groups. The lack of data on angiographic status of the foot arteries should be seen also as a major limiting factor in the analysis of these data. These studies predominantly included patients with diabetes and there is a lack of data on

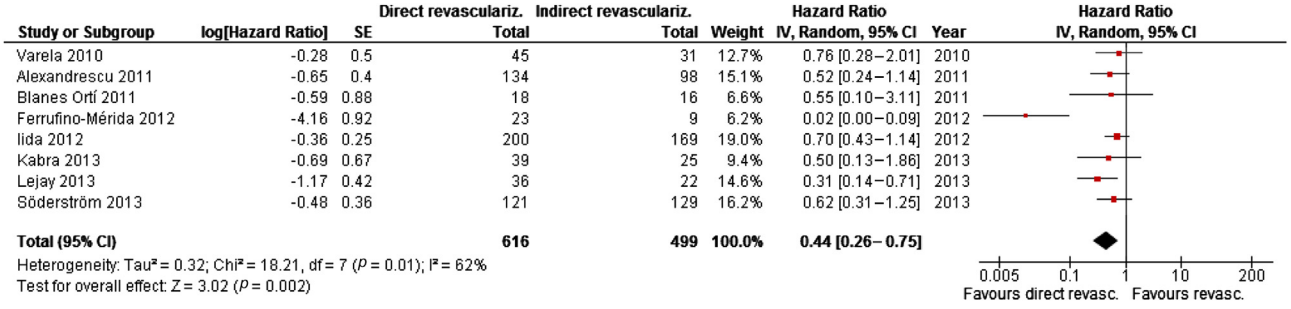


Figure 4. Forest plot for effectiveness of direct revascularization versus indirect revascularization according to the angiosome concept in limb salvage in patients with ischemic tissue lesions of the foot.

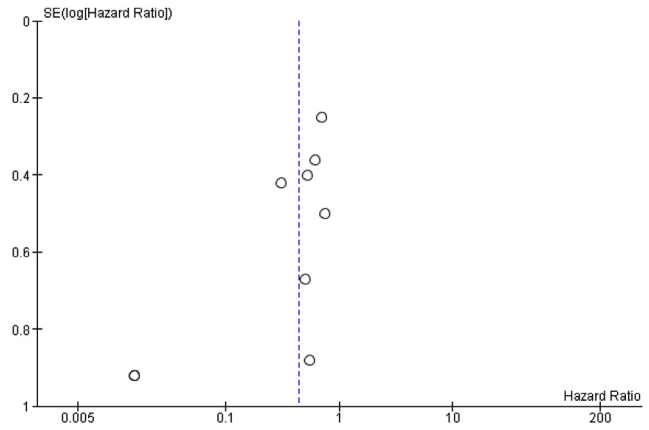
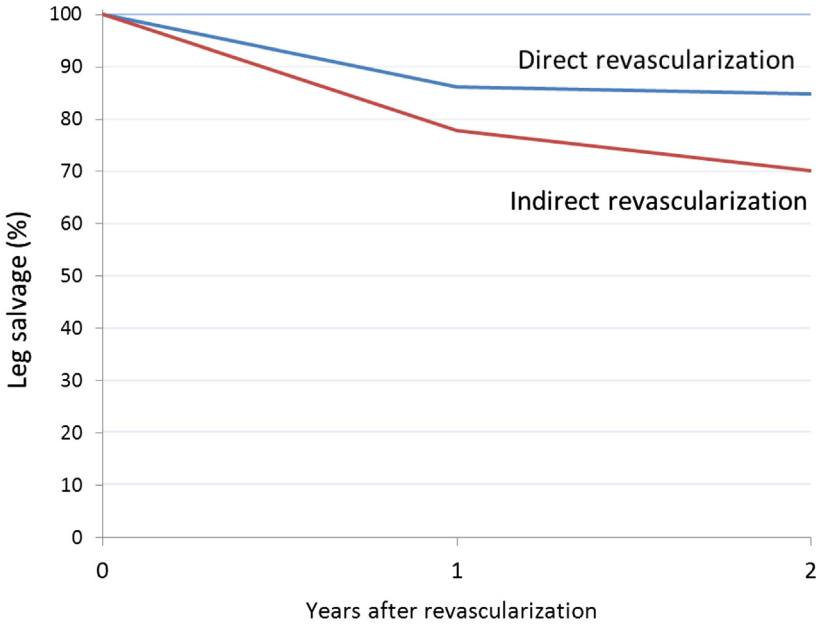


Figure 5. Funnel plot for effectiveness of direct revascularization versus indirect revascularization according to the angiosome concept in limb salvage in patients with ischemic tissue lesions of the foot.

the impact of angiosome-targeted revascularization in non-diabetic patients. Therefore, it is unclear whether this strategy is also effective in non-diabetic patients. In a recent systematic review,[19] some of these limitations were recognized as important. Indeed, these may prevent conclusive results on the validity of the angiosome concept.

Besides possible methodological issues affecting the results of the studies included here, there are also other technical issues which cannot be addressed in this meta-analysis. In fact, there is a lack of data on the feasibility of direct, angiosome-targeted revascularization in those patients who otherwise underwent indirect revascularization of the ischemic tissue lesions. This prevents any analysis of the outcome of those legs in which direct revascularization was not feasible and/or had possibly more diffuse atherosclerosis of the crural and foot arteries. In fact, the well established prognostic impact of the angiographic runoff status[20] might have influenced the results of this analysis. This explains why a few studies evaluating the impact of severity of atherosclerosis and of the status of the pedal arch and collateral circulation of the foot did not confirm the value of angiosome-targeted revascularization.[6,9] Beside these potential pitfalls, the results of this meta-analysis suggest that, when technically feasible, any revascularization attempt should be accomplished according to the angiosome principle as it seems superior to any indirect revascularization strategy. Future research should assess the feasibility of angiosome-targeted revascularization of the foot as well as the clinical and therapeutic implications in those patients in which direct revascularization is not feasible.

In conclusion, the results of the present meta-analysis suggest that, when feasible, direct revascularization of the foot angiosome affected by ischemic tissue lesions is



Direct revascularization			
Estimated legs at risk	554	238	124
Pooled leg salvage		86.2%	84.9%
95%CI		82.2-90.2	79.2-90.6
I^2		0%	0%
Indirect revascularization			
Estimated legs. at risk	465	177	72
Pooled leg salvage		77.8%	70.1%
95%CI		72.5-83.1	58.1-82.2
I^2		0%	49%

Figure 6. Pooled survival after direct and indirect revascularization according to the angiosome concept. Six studies were considered for estimation of 1-year limb salvage and five studies for 2-year limb salvage (estimated HR 0.55, 95% CI: 0.40–0.76).

associated with significantly higher rates of wound healing and limb salvage compared with indirect revascularization. Further studies of better quality, reporting on the angiographic status of the foot arteries, the characteristics of the wounds, all major outcome end-points, and adjusted analysis for differences between the study groups are needed to confirm the present findings.

CONFLICT OF INTEREST

None.

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None.

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