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Implications of target arterial path in foot perfusion and wound healing

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RESUMO

Introdução: A diabetes é atualmente um dos fatores de risco mais importantes para o desenvolvimento de doença arterial periférica. A associação da neuropatia, arteriopatia e alterações nos mecanismos de cicatrização conduz a uma maior predisposição para o desenvolvimento de úlceras nestes doentes. Vários sistemas de classificação foram desenvolvidos ao longo dos anos com o intuito de orientar uma melhor estratégia para gerir estes doentes. Em 1987, Taylor e Palmer introduziram o conceito de angiossoma. Este sistema divide a estrutura anatómica do corpo em blocos tridimensionais, cada um dos quais é vascularizado de forma única por artérias específicas. Ao longo dos últimos anos, os investigadores têm investido cada vez mais nos potenciais benefícios da revascularização orientada por angiossoma em indivíduos com isquemia crítica. O principal objetivo deste estudo é avaliar o impacto da revascularização dirigida por angiossoma no prognóstico de doentes diabéticos com isquemia critica.

Materiais e métodos: Avaliação retrospetiva de todos os doentes com pé diabético neuroisquémico provenientes da consulta multidisciplinar de pé diabético internados para estudo vascular invasivo e revascularização entre janeiro e dezembro de 2019 no Serviço de Angiologia e Cirurgia Vascular do Centro Hospitalar de Santo António. Dados demográficos e clínicos foram obtidos através da consulta do processo clínico de janeiro de 2019 a dezembro de 2023. O principal outcome foi o impacto de uma revascularização guiada por angiossoma na cicatrização da lesão trófica. Os outcome secundários foram: os diferentes fatores a influenciar a cicatrização, a avaliação da sobrevida livre de amputação e o impacto da estratégia de revascularização consoante a complexidade da doença arterial.

Resultados: Foram avaliados dados de 117 membros de 114 pacientes diabéticos com pé diabético neuroisquémico. Não houve diferença significativa entre a revascularização direta por angiossoma ou indireta na cicatrização aos 12 meses, contudo a revascularização direta parece associada a tempos de cicatrização menores. A severidade da infeção foi a única variável com impacto no tempo de cicatrização. A cirurgia endovascular não mostrou patência inferior à cirurgia aberta, mesmo em doentes maior complexidade de doença arterial (GLASS III).

Conclusão: Apesar de a revascularização guiada por angiossoma não ter mostrado taxas de cicatrização significativamente superiores aos 12 meses, parece haver uma tendência para uma cicatrização mais rápida.

Palavras-chave: Pé Diabético, Doença Arterial Periférica, Isquemia/Cirurgia, Sobrevida livre de amputação, Procedimentos Cirúrgicos Vasculares e Cicatrização de Feridas.

ABSTRACT

Introduction: Diabetes is currently one of the most important risk factors for the development of peripheral arterial disease. The coexistence of neuropathy, arteriopathy and alterations in healing mechanisms increases the risk of ulcer development in these patients. Various classification systems have been developed over the years to guide a better strategy for managing these patients. In 1987, Taylor and Palmer introduced the concept of angiosome. This system divides the body's anatomical structure into three-dimensional blocks, each of which is uniquely vascularized by specific arteries. Over the last years, researchers have increasingly invested in the potential benefits of angiosome-oriented revascularization in individuals with critical ischemia. The primary objective of this study is to evaluate the impact of angiosome-directed revascularization on the prognosis of diabetic patients with critical ischemia.

Materials and methods: Retrospective evaluation of all patients with neuroischemic diabetic foot from the multidisciplinary diabetic foot consultation admitted for invasive vascular study and revascularization between January and December 2019 at the Angiology and Vascular Surgery Department of Centro Hospitalar de Santo António. Demographic and clinical data were obtained by evaluating the clinical file from January 2019 to December 2023. The primary outcome was the impact of angiosome-guided revascularization on the healing of the trophic lesion. Secondary outcomes were: the different factors influencing healing, the assessment of amputation-free survival and the impact of the revascularization strategy depending on the complexity of the arterial disease.

Results: Data from 117 limbs of 114 diabetic patients with neuroischemic diabetic foot were evaluated. There was no significant difference between direct revascularization by angiosome and indirect revascularization in healing at 12 months. However, direct revascularization was associated with shorter healing times. The severity of the infection was the only variable with an impact on healing time. Endovascular surgery did not show inferior patency to open surgery, even in patients with more complex arterial disease (GLASS III).

Conclusion: Although angiosome-guided revascularization did not demonstrate significantly higher healing rates at 12 months, there appears to be a trend towards faster healing.

Keywords: Diabetic Foot, Peripheral Arterial Disease, Ischemia/Surgery, Limb Salvage, Vascular Surgical Procedures and Wound Healing.

LIST of ABBREVIATIONS

CI- Confidence Interval

DR- Direct Revascularization

FP – Femoropopliteal

GLASS- Global Limb Anatomic Staging System

GVGs - Global Vascular Guidelines

HR- Hazard Ratio

IP – Infrapopliteal

IR – Indirect Revascularization

LBP – Limb-Based Patency

PAD – Peripheral Artery Disease

STROBE - Strengthening the Reporting of Observational Studies in Epidemiology

TAP - Target Arterial Path

WIfI- Wound, Ischemia, and foot Infection

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INTRODUCTION

Diabetes is a significant risk factor for the development of peripheral arterial disease (PAD). These patients frequently exhibit concomitant peripheral neuropathy and altered healing mechanisms, increasing their risk of developing foot ulcers. PAD in diabetic patients is characterized by a bilateral multisegmentar disease pattern with predilection for the infragenicular arteries with impaired collateral formation.[1]

In 1987, Taylor and Palmer introduced the angiosome conceptual framework. This framework partitions the anatomical structure of the body into distinct three-dimensional blocks of tissue, each uniquely supplied by specific arteries. [2–6] This paradigm was initially applied in plastic surgery but has gained significant traction in the vascular field. Six angiosomes were identified in the foot, originating from the primary arteries.[2–4,7–10] The posterior tibial artery supplies three angiosomes to the plantar aspect of the foot, while the peroneal artery covers two angiosomes in the ankle and posterior foot. The anterior tibial artery supports the angiosome that spans the dorsum of the foot. The collateral vessel network between these angiosomes ensures uninterrupted blood flow through the foot if one or more arteries become occluded. [2–4,7–10] It is important to note that the distribution of the arterial tree in the leg and foot varies significantly among individuals, resulting in distinct angiosome territories that depend on the unique anatomical variations of each patient. [4,5,7]

Over the last fifteen years, scholars have increasingly investigated the potential benefits of angiosome-targeted revascularization for individuals with chronic ischemia. This includes both endovascular and open modalities.[11] Direct revascularization (DR) involves restoring a direct conduit for blood flow from the abdominal aorta to the specific angiosome associated with the wound, known as the 'wound-related artery.' In contrast, indirect revascularization (ID) reestablishes a direct conduit for blood flow to angiosome within the ankle or foot that are not affected by the tissue lesion. [4,7,11–14] The more recent Global Vascular Guidelines (GVGs) have introduced the concept of a Target Arterial Path (TAP). This path is defined as the optimal route within the arterial vasculature, designed to restore pulsatile blood flow to the ankle and foot in a seamless linear manner but it doesn’t consider angiosome concept.[15]

In addition to the selected revascularization pathway, it is also necessary to determine the optimal revascularization strategy. The choice between endovascular or surgical approach depends on various factors, such as the anatomical location and extent of disease, the availability of autologous conduit for bypass, patient comorbidities and functional status and intervention risk.[6,11,13] In sequence, the Global Limb Anatomic Staging System (GLASS) was developed. This system stratifies the patient according to the extent of infrainguinal arterial disease in order to estimate the chances of success of an endovascular revascularization and serves as guidance for the better approach. [16]

The aim of this study is to evaluate the implications of the arterial path and revascularization strategy on wound healing and limb salvage in diabetic patients treated in our Center.

MATERIALS AND METHODS

This retrospective single-center study includes patients with ischemic foot ulcers from the multidisciplinary diabetic foot unit and is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The study was approved by the Institutional Review Board and Ethics Committee. Due to the retrospective and purely observational nature of this study, which utilized anonymized data and had no impact on patient care, written informed consent was deemed unnecessary.

A search was conducted on PubMed using a range of search terms, including "Diabetic Foot," "Peripheral Arterial Disease," "Ischemia/Surgery," "Limb Salvage," "Vascular Surgical Procedures," and "Wound Healing". The articles included in the discussion were selected based on their publication date, relevance to the study and to ensure a diverse representation of results.

Inclusion Criteria

All patients from the multidisciplinary diabetic foot clinic with foot ulcer submitted to invasive vascular study and/or revascularization between January and December 2019 were included. The indications for an invasive angiographic study and revascularization included a foot ulcer in a patient with absent distal pulses and monophasic doppler waveforms, with one of the following: 1) TcPO2 <40mmHg or 2) TcPO2 40-60mmHg and a failing-to-heal lesion after four to six weeks of adequate wound care, foot offloading and infection control. The treatment approach was left to surgeon's discretion.

Data from January of 2019 to December of 2023 were collected. Database includes demographic, clinical and procedure-related details. Wound severity was evaluated according to the medical reports and classified using the Wound, Ischemia, and foot Infection (WIfI) System. [17]

All pre- and post-revascularization angiographies were analyzed and the complexity of the pre-revascularization was stratified according to the GLASS classification.[16] The presence or absence of an angiosome-directed revascularization was established according to the post-revascularization completion angiogram, considering the wound location. The patients with in-line flow to the wound corresponding angiosome were considered as direct revascularization. The matching outflow artery – wound location was defined as follows: 1) anterior tibial artery for ulcers located on the first and second toes or in the dorsal region; 2) posterior tibial artery for third to fifth toe and plantar lesions; 3) peroneal artery for heel wounds; all the others were considered as indirect revascularization.

The healing date was defined as the date of the first medical record in which full-thickness healing of the epidermis of the lesion was observed, including healing of the remaining foot tissue after debridement or minor amputation. Patients who did not achieve full-thickness healing during follow-up or were submitted to above the ankle amputation were considered as non-healing.

The limb-based primary patency of endovascular and surgical revascularizations was defined as the time from the index procedure until any reintervention in the circuit and compared among patients with low to moderate (GLASS I-II) vs. high (GLASS III) complexity arterial disease.

Outcomes

The primary outcome was to evaluate the relationship between angiosome directed-revascularization and wound-healing. Secondary outcomes included the assessment of amputation-free survival, limb-based patency of endovascular and open approach among different complexities of arterial disease and the establishment of potential predictors of impaired healing.

Statistical Analysis

The statistical analysis was conducted using IBM's SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA) with the 0.05 significance level being employed. Categorical data are expressed as frequencies and percentages, while non-categorical variables with a normal distribution are presented as means and standard deviations and non-categorical variables with a non-normal distribution are presented as median and interquartile range. The normality of continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. T-test or Mann-Whitney test were used to compare variables, depending on data distribution. Cox regression was employed to identify which variables were significantly associated with ulcer healing and limb-based patency. The occurrence of events over time was compared using Kaplan-Meier univariable analysis, and log-rank tests were performed to analyze the difference.

RESULTS

A total of 114 diabetic patients with ischemic foot ulcers, comprising 117 limbs, were evaluated. Most patients were male (n=83, 72.8%). The mean age of the patients was 68.8±9.9 years, with men being younger than women (68.1±10 versus 70.9±8.7). Only 8.8% (n=10) of patients were smokers, while 20.2% (n=23) had a history of smoking. 23.7% (n=27) had end-stage chronic kidney disease undergoing hemodialysis. Patient's baseline characteristics are described in table I.

A total of 160 ulcers were identified. The majority of lesions were limited to the forefoot (n=141, 88.1%), with most of them (n=126, 89.4%) being confined to the toes. The most prevalent lesion location was 1st toe (n=41, 25.6%), followed by 5th toe (n=24, 15.0%) and 2nd toe (n=22, 13.8%). 30.7% (n=35) of patients exhibited multiple ulcers. According to the WIfI classification, most patients were categorized as wound stage 1 (n=88, 55.0%), while 28.7% (n=46) and 16.3% (n=26) were classified as wound stages 2 and 3, respectively. 107 patients (66.9%) exhibited non-infected lesions (fI stage 0), while 27.5% (n=44) demonstrated mild to moderate local infection (fI stage 1 and 2). Only 5.6% (n=9) were classified as fI stage 3, with severe foot infection and a systemic inflammatory response. The characteristics of ulcers are summarized in table I.

Endovascular revascularization was performed in 70.9% (n=83) of cases, whilst conventional surgery was performed in 29.1% (n=34). Direct revascularization was performed in 57.3% (n=67), while indirect revascularization was performed in 42.7% (n=50).

Of the total number of limbs observed, 71 (60.7%) achieved successful healing. The median healing time was 155.5 days [96.5,155.5,331,8] in the DR group, comparing with 216 days [113,216,291] in the IR group. The healing times of the DR and IR groups were compared. No statistically significant difference was observed (p=0.915). The distribution of healing times for the DR and IR groups is shown in figure 1.

Comparing between direct or indirect revascularization by the 6th month, 41.8% of the DR healed, while 28% of the IR ischemic lesions had healed. In the course of one year, 62.7% of the DR lesions were cicatrized, in comparison to 62% of the IR lesions. Despite the observed differences in percentages, the resulting difference was not statistically significant (p = 0.819; Figure 2).

As shown in table II, after multivariate Cox regression analysis only the severity of foot infection significantly affected the time-to-healing (HR = 3.1, 95% CI [1.2;7.7], $p < 0.05$). None of the other variables evaluated (wound classification from WIfI, GLASS classification, Femoropopliteal (FP) and Infrapopliteal (IP) grades, Foot Predictor or angiosome-guided revascularization or not) reached statistical significance to impact the outcome.

73 limbs underwent minor amputations and 29 limbs underwent above-the-ankle amputations. The 6- and 12-month amputation-free survival was 77.4% and 69.8% in the DR group,

comparing with 72% and 64% in the IR group, respectively, with no statistical difference between them (p = 0.563, Figure 3).

The 12- and 24-month limb-based patency (LBP) for open surgery was 82.4% and 73.5%, comparing with 12-month LBP of 83.1% in the endovascular group, sustained by the 2nd year of follow-up, with no statistical difference between them (p=0.235, Figure 4). Subgroup analysis according to disease severity (GLASS I and II vs. GLASS III) showed 12- and 24-months LBP of 81.8% for open surgery and 88.6% for endovascular approach in the GLASS I-II patients, with no statistical difference between them (p=0.837, Figure 5). When analyzing higher complexity patterns of disease (GLASS III), the 12- and 24-months LBP was 78.3% and 65.2% in the open surgery group and 76.9% in the endovascular group, also without statistical difference between approaches (p=0.348, Figure 6).

Following multivariate Cox regression analysis, neither the GLASS stage nor other potential confounders, including the Foot Predictor, postoperative antithrombotic regimen and revascularization approach, significantly affected the limb-based patency, as table III shows.

DISCUSSION

Patients with peripheral artery disease who develop trophic lesion should be evaluated and stratified according to the WIfI classification to guide the need for revascularization.[13,17] However, the selected approach may not be linear, particularly in this population of frail patients with multisegmentar and distal arterial disease. Some studies have indicated that angiosome-targeted revascularization may be beneficial, particularly in diabetic patients with a high prevalence of inframalleolar arterial disease, a lack of complete pedal arch and consequently poor vascular connections between angiosomes.[9,18,19] The most recent CLTI guidelines introduced the concept of Target Arterial Path, stating that in patients requiring revascularization attempts should be made to establish in-line flow to the foot (Good Practice Statement).[13] Nevertheless, the advantages of an angiosome-guided revascularization approach remain unproven. Consequently, the guidelines advise that this strategy may be considered, although there is currently no solid evidence to support it (recommendation grade 2, level C). [13] The results obtained in this study are in agreement with those previously reported, indicating that there is no significant difference in wound healing and amputation-free survival between patients who received direct or indirect angiosome revascularization.[6,9,19] However, patients who underwent direct angiosome revascularization exhibited accelerated healing, with 41.8% of patients achieving complete healing by the 6th month and a median time to healing of 155 days in the DR group, in comparison to 28% of healed lesions by the 6th month, with a median time of 216 days in the IR group. This is readily comprehensible in light of the more direct blood supply to the wound, which may potentially accelerate the healing process. It also reveals a potential advantage of angiosome-directed revascularization, whereby the total time for successful cicatrization is minimized, thus reducing the associated morbidity and costs.[9,18–21]

A multivariate analysis revealed that the severity of foot infection was the only variable with a significant impact in wound healing. Improvement of the efficient control of infection will result in reduction of ulcer time healing rate, thereby improving the patient's survival rate and subsequent healing of the lesion. [18,22]

The endovascular approach demonstrated superior 12- and 24-month primary limb-based patency when compared to conventional surgery. However, the difference was not statistically significant ($p=0.235$). This may be partially justified by the smaller sample size in the surgical group, the potentially higher complexity of the arterial disease and the wound status in the surgical group. Nonetheless, even when comparing between endovascular and conventional approaches among the same high-complexity GLASS III patients, the endovascular group did not perform worse. These results contrast the current guidelines, which defends 12-month LBP <50% for GLASS III patients submitted to an endovascular treatment.[13] It is, however, crucial to recognize that the suboptimal outcomes reported in the literature for endovascular treatment of complex lesions are likely to be a reflection of the initial basic endovascular techniques and not to have taken into account the improved and most recent results with the constantly developing endovascular techniques and devices. Additionally, endovascular intervention may be the preferred option for high-risk patients who are eligible for revascularization due to the reduced surgical risk associated with this procedure.[6,13,19] The surgical open approach remains the most effective solution for many patients, and when the patient has a suitable autologous conduit, it continues to be the superior option in terms of long-term patency.[6,10,13] The results of this study did not demonstrate a clear superiority of the surgical group as previously stated. It is, however, important to note that the type of revascularization and conduit were not analyzed independently. Also, the surgical patients maintain a closest follow-up after wound-healing for bypass surveilling what may lead to more reinterventions which will impact the limb-based patency.

Despite the conflicting results observed in previous studies comparing the different surgical approaches, the authors conclude that open and endovascular surgery have a complementary role, particularly in patients with multisegmentar disease. [5,13] Bypass surgery may be easily employed to overcome the unsuccessful crossing of an occluded vessel, which represents the main limitation of endovascular techniques.[4,8,10,23] In contrast, endovascular treatment has the advantage of potentially reaching vessels that are not suitable for adequate bypass landing and with lesser morbidity for the patient.[6,13,24]

Certain limitations must be taken into account when considering the results of the study. The single-center retrospective design may have introduced a selection bias, limiting the ability to infer causality between the variables studied. Moreover, the sample size was insufficient to allow analysis of potentially significant variables. The wound healing process is a complex phenomenon that involves a multitude of mechanisms beyond the status of foot perfusion. This complexity may hinder the true implications of revascularization. The most appropriate wound care, offloading and medical treatment were provided to all patients in accordance with the center's protocol. However, it was not possible to evaluate patient compliance. Additionally, a systematic evaluation of the TAP was not conducted, except in patients with bypasses or in those whose lesions failed to heal properly. This may result in artificially elevated long-term patency rates, particularly in the endovascular group. However, the weight of this outcome is reduced after successful wound healing in this group, as the revascularization procedure achieves its intended goal.

CONCLUSION

There was no statistically significant difference between direct and indirect revascularization in terms of ulcer healing and amputation-free survival. Patients in whom angiosome-directed revascularization was performed appeared to heal more promptly. It is evident that a foot infection has a significant impact on wound healing, regardless of the revascularization status. Consequently, it is imperative to implement an aggressive infection control strategy, including antibiotic therapy and effective wound debridement, in addition to the revascularization procedures.

Regardless of disease severity, limb-based patency was similar between the endovascular and open surgery groups, in contrast to previous literature. This reflects the more effective endovascular techniques, overcoming previous limitations and broadening the spectrum of patients who may benefit from this approach. Future research should be conducted with a more systematic evaluation of patient, wound and foot perfusion status to overcome the limitations of this study.

APPENDIX

Table I. Patient's baseline characteristics.

Data are presented as n (%) and mean ± standard deviation.

Patients	114
Limbs	117
Male sex	83 (72.8)
Age	68.8±9.9
Male	68.1±10
Female	70.9±8.7
Smoking history	
Smokers	10 (8.8)
Ex-smokers	23 (20.2)
Non-smokers	81 (71.1)
End-stage chronic kidney disease	27 (23.7)
Lesions	160
Local of lesion	
Forefoot	141 (88.1)
Hindfoot	16 (10.0)
Leg	3 (1.9)
Wound stage	
1	88 (55.0)
2	46 (28.7)
3	26 (16.3)
foot Infection stage	
0	107 (66.9)
1	17 (10.6)
2	27 (16.9)
3	9 (5.9)

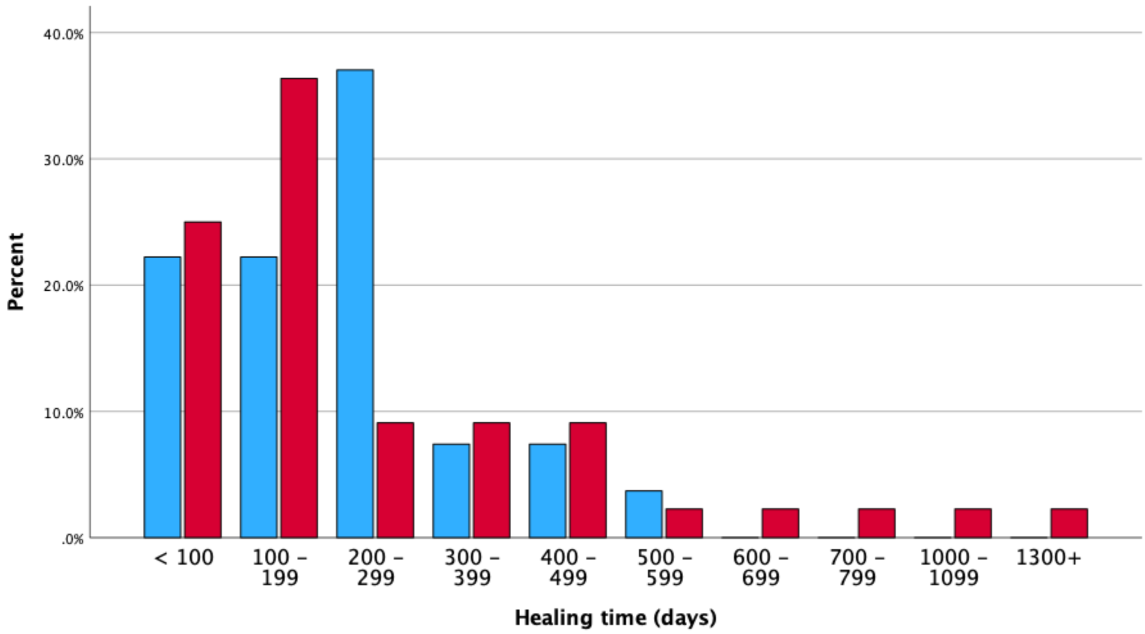

Figure 1. Proportion of ulcers healed by time, grouped into 100-day intervals, for IR and DR groups.

Blue columns: indirect revascularization; Red columns: direct revascularization.

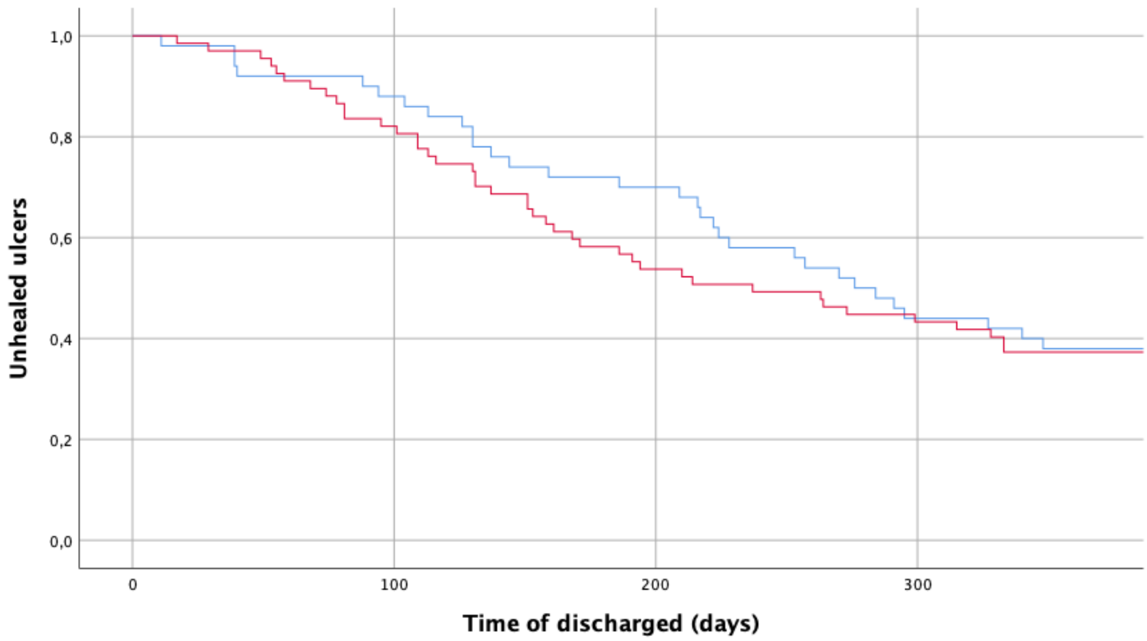

Figure 2. Kaplan-Meier curves comparing ulcer healing at 365 days.

Blue line: indirect; Red line: direct revascularization.

Table II. Stepwise backwards multivariate Cox regression for predictor of ulcer healing time.

	HR	p	95% CI	HR	p	95% CI
Angiosome-guided Revascularization (or not)	0.5	0.2	0.2 - 1.3			
Foot Predictor 1	1.1	0.9	0.1 - 9.0			
Foot Predictor 2	0.7	0.7	0.2 - 3.4			
GLASS stage	0.5	0.4	0.1 - 2.1			
FP grade	2.3	0.1	0.8 - 7.3			
IP grade	0.8	0.7	0.2- 2.9			
Wound 1- WIfI	0.0	1	0			
Wound 2- WIfI	0.0	1	0			
foot Infection - WIfI	3.2	0.04	1.1 - 9.9	3.1	0.02	1.2-7.7

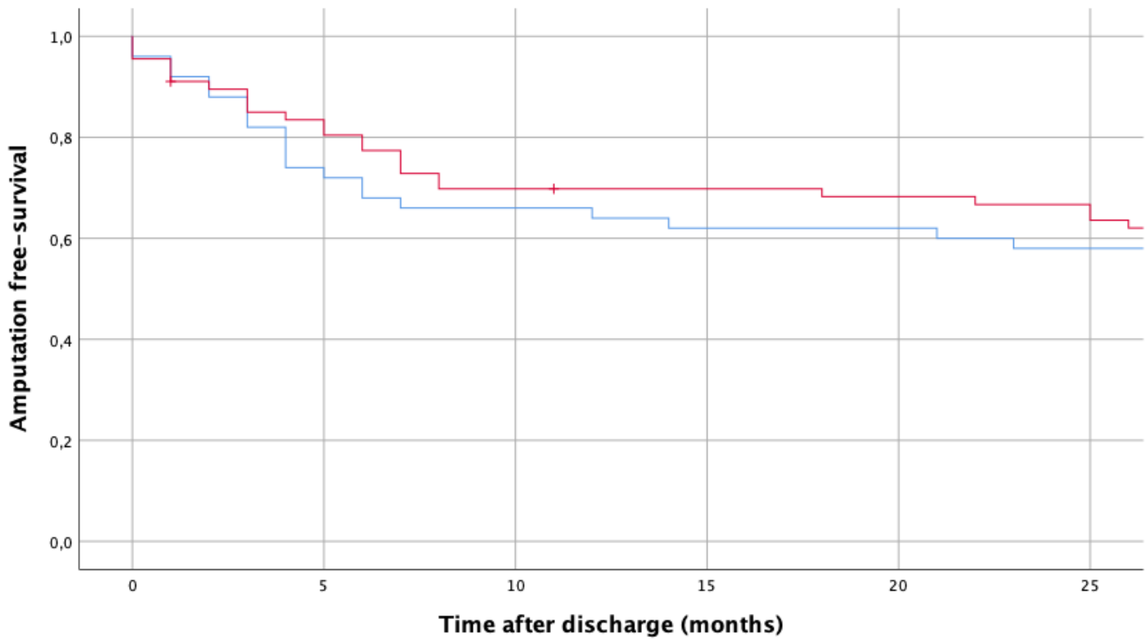

Figure 3. Kaplan-Meier curves comparing amputation free-survival at 25 months.

Blue line: indirect revascularization; Red line: direct revascularization.

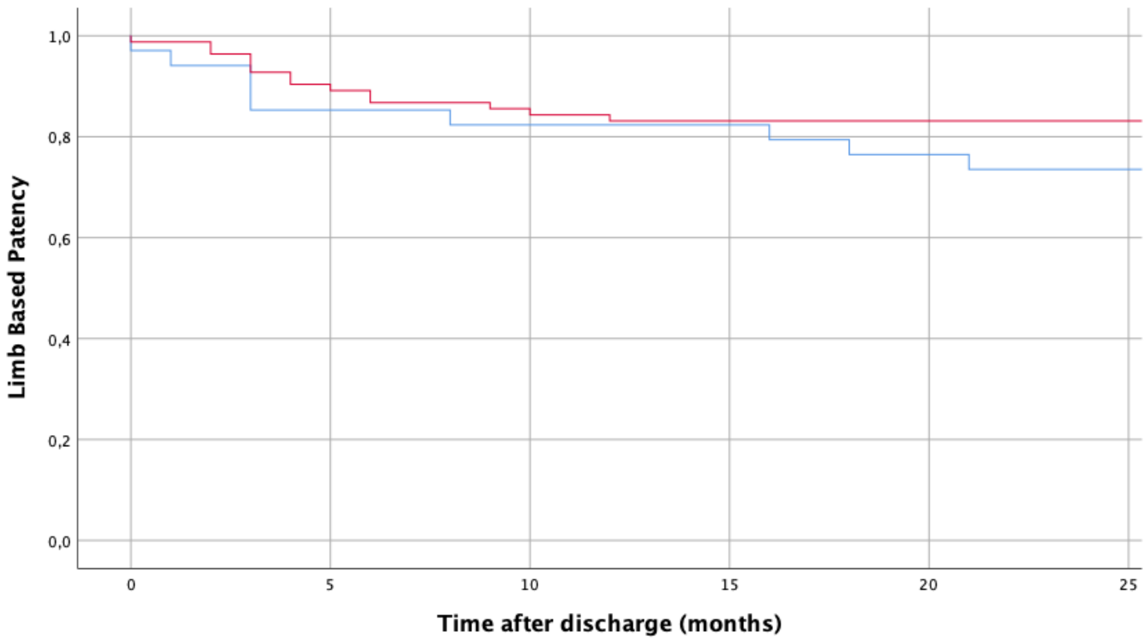

Figure 4. Kaplan-Meier curves comparing overall limb-based patency between conventional surgery and endovascular therapy at 25 months.

Blue line: conventional surgery; Red line: endovascular therapy.

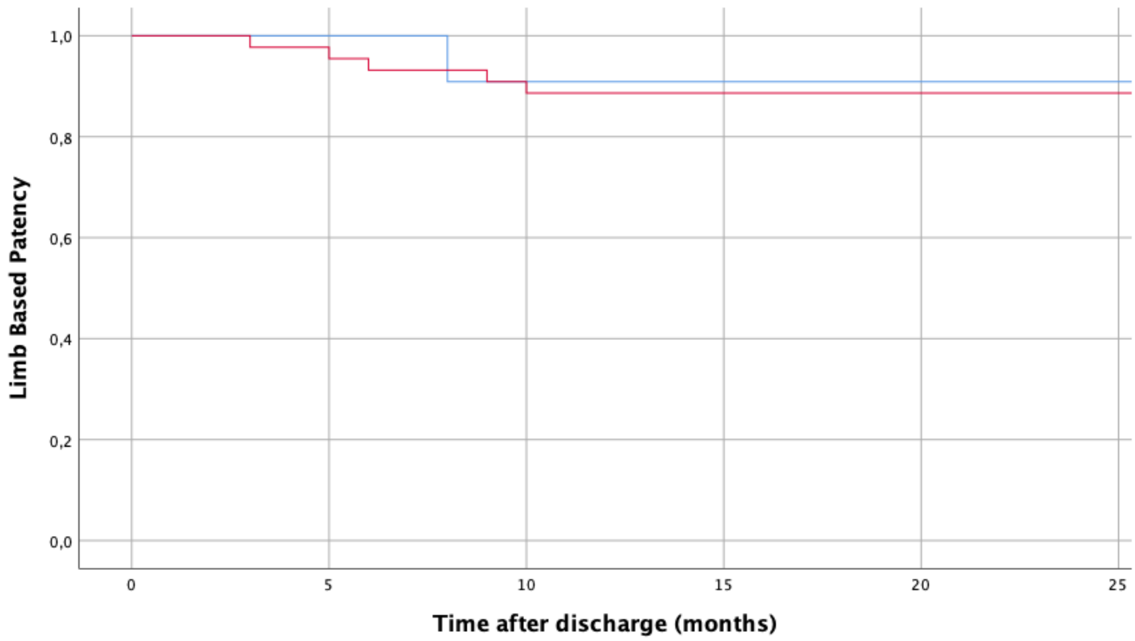

Figure 5. Kaplan-Meier curves comparing limb-based patency between GLASS 1-2 conventional surgery and GLASS 1-2 endovascular therapy at 25 months.

Blue line: conventional surgery; Red line: endovascular therapy.

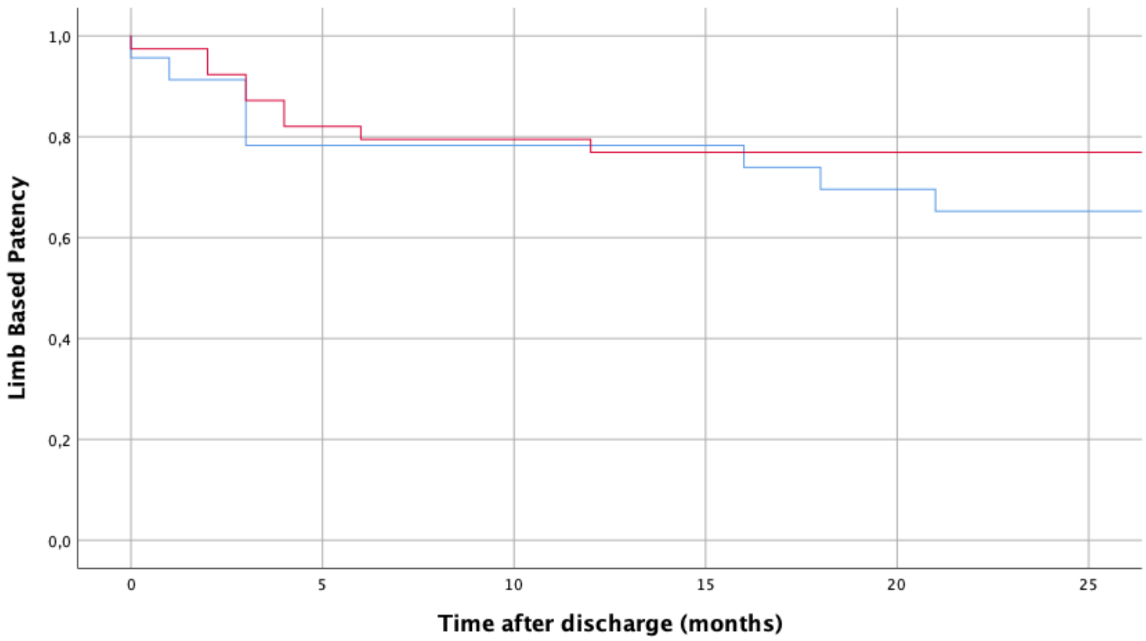

Figure 6. Kaplan-Meier curves comparing overall limb-based patency between GLASS 3 conventional surgery and GLASS 3 endovascular therapy groups at 25 months.

Blue line: conventional surgery; Red line: endovascular therapy.

Table III. Stepwise backwards multivariate Cox regression for predictor of limb-based patency.

	HR	p	CI
Foot Predictor 1	0.7	0.6	0.2 - 2.6
Foot Predictor 2	0.4	0.1	0.1 - 1.1
GLASS stage	0.6	0.2	0.3 - 1.4
Pos-OP Therapy	0.7	0.5	0.3 - 1.7
Revascularization (Surgery VS Endovascular)	1.2	0.6	0.5 - 3

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