Eur J Vasc Endovasc Surg (xxxx) xxx, xxx

# Impact of Infrapopliteal Revascularisation Establishing In Line Flow to the Wound in Patients with Chronic Limb Threatening Ischaemia

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**WHAT THIS PAPER ADDS**

This study, using a core laboratory for assessing wounds and in line flow, revealed that infrapopliteal revascularisation establishing in line flow to the wound (IFW) had a higher wound healing rate than that not achieving IFW, regardless of revascularisation strategy (bypass grafting or endovascular procedure), in patients with chronic limb threatening ischaemia. Whether revascularisation was direct or indirect according to the classical angiosome concept did not affect the superiority of IFW. In determining target vessels to be revascularised, personalised angiographic assessment of in line flow including collateral circulation would be more important than conceptualised and standardised angiosome maps of the foot.

**Objective:** This study aimed to determine the impact of infrapopliteal (IP) revascularisation establishing in line flow to the wound (IFW) on wound healing in chronic limb threatening ischaemia (CLTI), using a core laboratory assessment for wounds and in line flow.

**Methods:** The Wound directed Angiosome RevasculaRIsation apprOach to patients with cRitical limb iSchaemia (WARRIORS) multicentre observational study enrolled patients with CLTI with tissue loss undergoing IP revascularisation in Japan, with scheduled two year follow up. The primary outcome measure was complete wound healing, defined as achievement of complete epithelialisation of all wounds without major amputation. IP revascularisation establishing IFW was defined as revascularisation after which a tibiopedal artery that actually fed an injured pedal unit was patent. The incidence of wound healing was compared between the IFW and non-IFW groups using inverse probability of treatment weighting based on the propensity score.

**Results:** A total of 440 patients with CLTI (median age, 75 years; male, 64.1%; diabetes mellitus, 72.0%; dialysis, 57.7%) with tissue loss (Wound, Ischaemia, and foot Infection stage 4, 66.4%) who underwent IP revascularisation (endovascular procedure, $n = 304$; bypass grafting, $n = 136$) between October 2017 and June 2020 were registered. During a median follow up of 23.6 months, 51.1% achieved wound healing. Successful IP revascularisation with IFW was achieved in 68.2%. After analysis, the IFW group had a higher rate of wound healing than the non-IFW group (34.5 *vs.* 16.1 per 100 person years; $p = .030$). The association between IFW and wound healing was not statistically different between patients undergoing bypass grafting and those undergoing an endovascular procedure ($p$ for interaction = .38). There was no statistically significant interaction effect between IFW and direct revascularisation for wound healing ($p$ for interaction = .51).

**Conclusion:** IP revascularisation establishing IFW was statistically significantly associated with a higher wound healing rate in patients with CLTI.

**Keywords:** Angiosome, Bypass grafting, Chronic limb threatening ischaemia, Endovascular procedure, Infrapopliteal, In line flow
Article history: Received 10 December 2023, Accepted 22 July 2024, Available online XXX


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https://doi.org/10.1016/j.ejvs.2024.07.024

## INTRODUCTION

Chronic limb threatening ischaemia (CLTI) is the most severe manifestation of atherosclerotic lower extremity arterial disease.[1] Approximately half of patients with CLTI will die or lose their limb if blood flow in the index limb is not appropriately restored.[2] The distribution of arterial lesions in the lower extremity is generally affected by atherosclerotic risk factors. Advanced age, diabetes mellitus, and end stage renal disease are more likely to be associated with infrapopliteal (IP) lesions.[3] The prevalence of these risk factors has increased in recent years, and a growing number of patients with CLTI now require IP revascularisation.[4]

The traditional goal of IP revascularisation for ischaemic wounds was to establish in line flow to the foot.[2,4] Recently, several studies have suggested that in line flow to the wound (IFW) would be more important to achieve wound healing.[5,6] While the concept of IFW is theoretically satisfying, the quality of its evidence was suboptimal; the judgement of IFW in those previous studies was not based on a core laboratory assessment of ischaemic wounds and vascular imaging, thus lacking objectivity in their findings. The current study used a core laboratory for assessing wounds and in line flow and evaluated the impact of IP revascularisation establishing IFW on wound healing in patients with CLTI.

## MATERIALS AND METHODS

### Study design and participants

The Wound directed Angiosome RevasculaRIsation apprOach to patients with cRitical limb iSchaemia (WARRIORS) study was a multicentre, observational, core laboratory adjudicated study that prospectively enrolled patients who presented with CLTI with tissue loss caused by atherosclerotic arterial disease at 23 centres (including 14 vascular surgery departments and 16 interventional cardiology departments) in Japan. Study patients were scheduled to be followed up for two years. The inclusion criteria for this study were patients who (1) were $\geq$ 20 years of age, (2) had an ischaemic wound with skin perfusion pressure of $<$ 40 mmHg, and (3) were planned for IP arterial revascularisation using either vein bypass or an endovascular procedure. Exclusion criteria included (1) patients with CLTI primarily caused by non-atherosclerotic chronic vascular conditions of the lower extremity, and (2) those with extensive ischaemic ulcers or gangrene beyond the ankle joint, where limb salvage was deemed impractical even with revascularisation or major amputation was already scheduled. Non-atherosclerotic chronic vascular conditions were diagnosed with comprehensive evaluation incorporating both clinical assessment and advanced laboratory examination, alongside angiographic visualisation, adhering to the respective diagnostic criteria established for each disease. This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the participating centres. Informed consent was obtained from the participants or, if not possible, from their family.

### Evaluation of baseline characteristics

Registration was in advance of IP revascularisation. Prior to revascularisation, patient baseline characteristics, lower limb condition, and anatomical severity were evaluated. The Wound, Ischaemia, and foot Infection (WIfI) classification system was employed to evaluate wounds in the index limb. The severity of ischaemia was evaluated by skin perfusion pressure. The skin perfusion pressure was measured using a dedicated device (PAD 4000; Kaneka Medical Products, Osaka, Japan).[7] The anatomical location and severity of arterial lesions were routinely assessed using duplex ultrasound as a non-invasive test. If arterial disease detected by duplex ultrasound was haemodynamically significant, the presence of a significant arterial lesion was diagnosed by digital subtraction angiography (DSA) prior to revascularisation. The treatment strategy by either bypass or endovascular procedure was determined by vascular specialists including vascular surgeons and interventional cardiologists in each local hospital according to clinical practice. The target artery for revascularisation was chosen primarily based on the angiosome concept if anatomical and technical feasibility was achievable. Each hospital could select both bypass and endovascular procedures. Bypass was performed using saphenous vein grafts, and an endovascular procedure was performed using non-coated balloon angioplasty. The follow up protocol largely relied on the routine of participating hospitals, but was generally scheduled every two to four weeks until complete wound healing and every three months thereafter until the patient was able to visit their hospital. The WARRIORS study scheduled follow up of study patients for two years. The final follow up assessment was scheduled at 24 months with a tolerance of $\pm$2 months.

### Wound and angiographic core laboratory assessment

The study prospectively collected wound photographs and completion angiograms to evaluate wounds and in line flow at a core laboratory. The location and severity of the wound prior to revascularisation was judged based on photographs taken at each participating hospital. The foot was photographed from both the dorsal and plantar sides, capturing the entire foot. Additionally, a close up photograph was taken to provide a more detailed assessment of the wound. A plastic surgeon at the core laboratory judged the WIfI W and fI grades based on the photographs, blinded to angiographic information. In line flow after IP revascularisation was evaluated based on the completion angiogram, which was taken by DSA and standardised according to the imaging protocol including the assessment of IP and inframalleolar anatomical condition. Two vascular specialists (one endovascular interventionist and one vascular surgeon) at the core laboratory identified the location of wounds by pedal photographs and judged IFW based on completion angiograms (the endovascular interventionist evaluated endovascular cases and the vascular surgeon evaluated bypass cases). IFW was defined as revascularisation after which a tibiopedal artery that actually fed an injured pedal unit was patent (Fig. 1).

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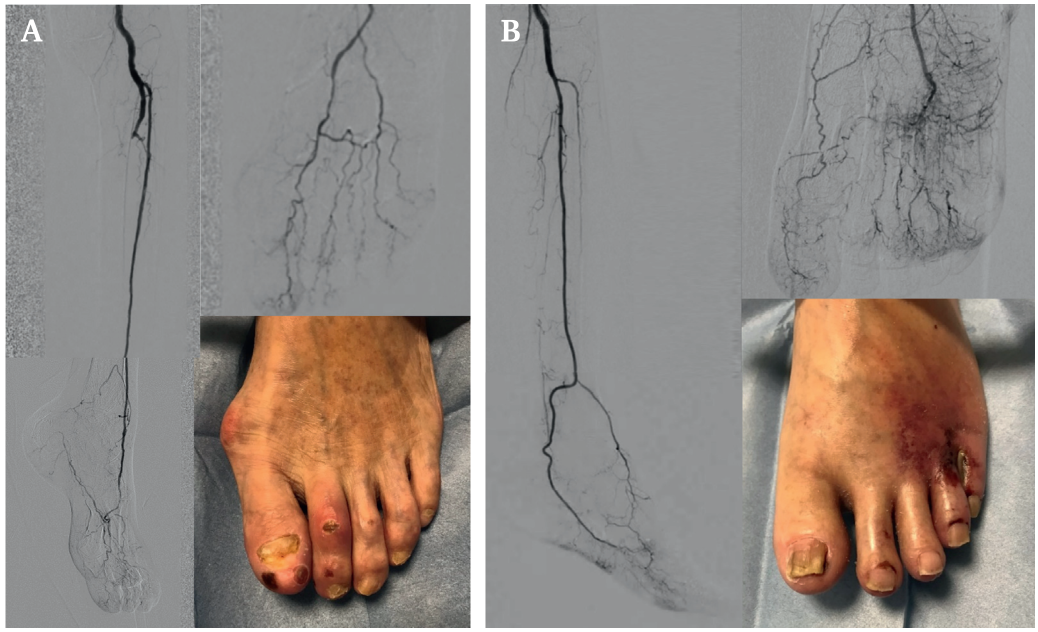


**Figure 1.** Representative case of infrapopliteal revascularisation establishing in line flow to the wound. (A) Successful revascularisation of the anterior tibial artery directly supplying blood flow to the first and second toes. (B) Successful revascularisation of the peroneal artery directly supplying blood flow to the fourth and fifth toes.

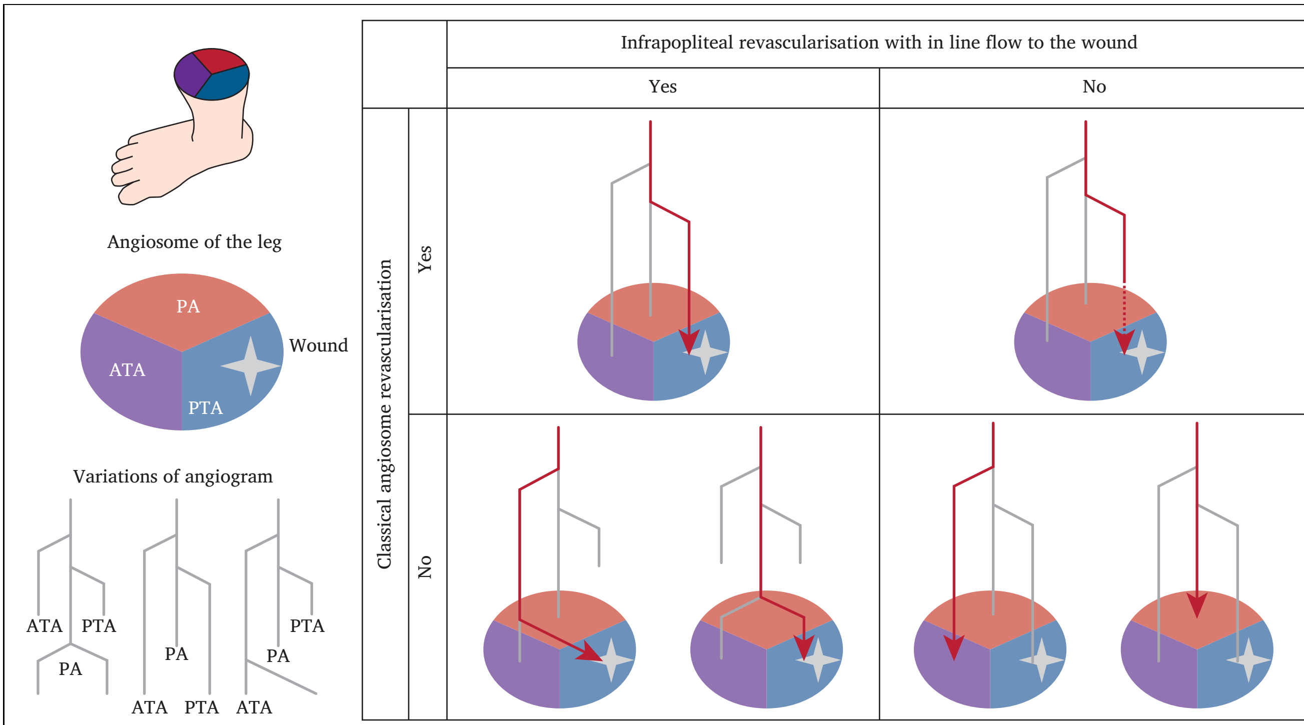


**Figure 2.** Definition of infrapopliteal (IP) revascularisation establishing in line flow to the wound (IFW) in contrast to classical angiosome guided revascularisation. Take an ischaemic wound located in the pedal unit, which is theoretically fed by the posterior tibial artery (PTA) according to the classical angiosome concept, for example (as schematised in the left upper panel). Collateral circulation can be developed in the network of tibiopedal arteries; the left lower panel demonstrates some anatomical patterns of the IP angiogram. The right box shows the matrix diagram of IP revascularisation establishing IFW and classical angiosome guided revascularisation. Classical angiosome guided revascularisation indicates revascularisation for the PTA, but not the anterior tibial artery (ATA) or peroneal artery (PA); whereas IP revascularisation establishing IFW is revascularisation of the artery directly perfusing the wound. Classical angiosome guided revascularisation is not always concordant with personalised angiosome guided revascularisation.

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The core laboratory also evaluated whether IP revascularisation was direct according to the classical angiosome concept, which was defined as revascularisation after which a tibial artery conceptually feeding an injured pedal unit was patent. The classical angiosome was based on the idea that the foot could be anatomically divided into units according to three feeding arteries in the lower leg: the anterior tibial artery (ATA); the posterior tibial artery (PTA); and the peroneal artery. The dorsum of the foot was the unit supplied by the ATA, while the lateral anterior upper ankle and the lateral and plantar sides of the heel were the units supplied by the peroneal artery. The medial heel, instep, lateral midfoot, and forefoot were the units supplied by PTA.[8] The toes were the units that could be supplied by either the ATA or PTA. The patency of the IP artery was defined as in line non-delayed flow without arterial stenosis (Fig. 2).

### *Outcome measure*

The primary outcome measure was complete wound healing, which was defined as achievement of complete epithelialisation of all wounds without major amputation. The incidence of wound healing after two years was compared between the groups with and without IFW.

### *Statistical analysis*

Data on baseline characteristics are presented as the median and interquartile range (IQR) for continuous variables and as frequency and percentage for categorical variables, unless otherwise stated. A two sided $p$ value of $< .050$ was considered statistically significant, and 95% confidence intervals (CIs) are reported where appropriate. Values were not corrected for multiple hypothesis testing. When patients in whom IFW was achieved (IFW group) were compared with those in whom IFW was not achieved (non-IFW group), inverse probability of treatment weighting (IPTW) based on the propensity score was used to minimise intergroup differences in baseline characteristics. Since revascularisation strategies during the IP endovascular procedure were expected to be distinct from those during bypass, the propensity score for IP endovascular cases and that for bypass cases was developed separately from each other. The propensity score was calculated using a logistic regression model. The following explanatory variables were included in the model: age; sex; mobility; smoking; renal failure on dialysis; diabetes mellitus; history of IP revascularisation; loss of protective sensation; severity of CLTI evaluated with the WIfI classification; and femoropopliteal endovascular procedure. Differences in baseline characteristics between groups were tested using the linear regression model for continuous variables, the binary logistic regression model for dichotomous variables, and the ordinal logistic regression model for ordinal variables, while intergroup differences in time to events were tested using the Poisson regression model. The IP revascularisation strategy (bypass grafting or endovascular procedure) was entered as the covariable in the regression models. The Poisson regression model was also used to investigate the interaction effect of baseline characteristics on the association between IFW and wound healing. The association between IFW achieved revascularisation and direct revascularisation according to the classical angiosome was additionally examined. Missing data were addressed using multiple imputation by the chained equations (MICE) method. During the procedure, five imputed datasets were generated and the analytic results were combined according to Rubin's rule. All statistical analyses were performed using R version 4.1.1 (R Development Core Team, Vienna, Austria).

## RESULTS

A total of 440 patients with CLTI with tissue loss underwent IP revascularisation between 11 October 2017 and 30 June 2020. Baseline characteristics of the study population are summarised in Table 1. Baseline characteristics of patients

**Table 1. Baseline characteristics of the study population ($n$ = 440).**

| Characteristic | Patients ($n$ = 440) |
|---|---|
| Age – y | 75 (68, 81) |
| Male sex | 282 (64.1) |
| Non-ambulatory | 225 (51.1) |
| Smoking history | 253 (57.5) |
| Renal failure on dialysis | 254 (57.7) |
| Diabetes mellitus | 317 (72.0) |
| History of distal bypass | 9 (2.0) |
| History of infrapopliteal endovascular procedure | 99 (22.5) |
| *Loss of protective sensation* | 141 (36.9) |
| Missing data | 58 (13.2) |
| *WIfI clinical stage* | |
| Stage 2 | 20 (4.7) |
| Stage 3 | 123 (28.9) |
| Stage 4 | 282 (66.4) |
| Missing data | 15 (3.4) |
| *WIfI W grade* | |
| Grade 1 | 180 (42.4) |
| Grade 2 | 191 (44.9) |
| Grade 3 | 54 (12.7) |
| Missing data | 15 (3.4) |
| *WIfI I grade* | |
| Grade 2 | 97 (22.0) |
| Grade 3 | 343 (78.0) |
| *WIfI fI grade* | |
| Grade 0 | 73 (17.2) |
| Grade 1 | 128 (30.1) |
| Grade 2 | 207 (48.7) |
| Grade 3 | 17 (4.0) |
| Missing data | 15 (3.4) |
| *Femoropopliteal endovascular procedure* | 162 (36.8) |
| Stent implantation | 75 (17.0) |
| Drug technology | 62 (14.1) |
| *Establishing in line flow to the wound* | 249 (68.2) |
| Missing data | 75 (17.0) |

Data are presented as median (interquartile range) or $n$ (%). WIfI = Wound, Ischaemia, and foot Infection.

with and without data missing are shown in Supplementary Table S1. The mean patient age ± standard deviation was 74 ± 9 years, with a high prevalence of comorbidities such as diabetes mellitus (72.0%, $n = 317$) and renal failure on dialysis (57.7%, $n = 254$). WIfI clinical stage 4 accounted for 66.4% ($n = 282$) of the limbs. Bypass grafting was performed in 30.9% of patients ($n = 136$), while an endovascular procedure was employed in 69.1% ($n = 304$). IFW was achieved in 68.2% ($n = 249$). Two year follow up was completed in 91.8% ($n = 404$), and the follow up index was calculated to be 0.95 ± 0.19. During a median follow up of 23.6 (IQR 11.8, 24.5) months, 225 patients (51.1%) achieved wound healing.

### *Comparison between patients with and without in line flow to the wound*

The baseline characteristics in the IFW and non-IFW groups are shown in Table 2. Before IPTW, IFW was more likely to be achieved in older patients, who tended to be free from dialysis and have a lower WIfI W grade. After IPTW, there were no statistically significantly intergroup differences in baseline characteristics (Table 2). Standardised differences are shown in Supplementary Table S2. The IFW group had a higher incidence of wound healing than the non-IFW group (34.5 [95% CI 23.7 − 50.2] *vs.* 16.1 [95% CI 8.5 − 30.5] per 100 person years; $p = .030$), with an incidence risk ratio of 2.13 (95% CI 1.08 − 4.20) (Table 3). Death was not statistically significantly different between the groups ($p = .18$). Figure 3 illustrates the Kaplan−Meier estimates of cumulative wound healing and overall survival. The association between IFW and wound healing was not statistically significantly different between the bypass and IP endovascular procedure groups ($p$ for interaction = .38) (Fig. 4). Moreover, no other baseline characteristic had a statistically significant interaction effect on the association between IFW and wound healing (all $p$ for interaction > .050).

### *Association with direct revascularisation according to the classical angiosome*

The proportion of direct revascularisation according to the classical angiosome concept was 62.7% in the IFW group and 53.2% in the non-IFW group after IPTW ($p = .16$). In the IFW group, the incidence of wound healing was not statistically significantly different between patients with and without direct revascularisation; the incidence risk ratio was 1.19 (95% CI 0.52 − 2.76; $p = .68$). Similarly, the incidence

**Table 2.** **Baseline characteristics of patients with and without in line flow to the wound (IFW) before and after inverse probability of treatment weighting (IPTW).**

| Characteristic | Before IPTW | | | After IPTW | | |
|---|---|---|---|---|---|---|
| | Non-IFW group ($n$ = 146.8) | IFW group ($n$ = 293.2) | $p$ value | Non-IFW group ($n$ = 146.8) | IFW group ($n$ = 293.2) | $p$ value |
| Age − y | 73 (66, 79) | 76 (69, 82) | .034 | 75 (67, 80) | 75 (68, 81) | .86 |
| Male sex | 68.7 | 61.8 | .20 | 66.2 | 64.5 | .75 |
| Non-ambulatory | 49.7 | 51.8 | .64 | 54.1 | 51.9 | .69 |
| Smoking history | 59.9 | 56.3 | .56 | 59.6 | 57.6 | .72 |
| Renal failure on dialysis | 63.9 | 54.6 | .062 | 56.3 | 57.0 | .90 |
| Diabetes mellitus | 73.7 | 71.2 | .70 | 72.2 | 72.5 | .95 |
| History of distal bypass | 2.4 | 1.8 | .90 | 1.4 | 1.8 | .75 |
| History of infrapopliteal endovascular procedure | 24.8 | 21.4 | .38 | 21.8 | 22.6 | .86 |
| Loss of protective sensation | 39.5 | 37.7 | .81 | 38.8 | 38.1 | .92 |
| *WIfI clinical stage* | | | .40 | | | .89 |
| Stage 2 | 3.7 | 5.6 | | 3.6 | 5.2 | |
| Stage 3 | 26.8 | 29.7 | | 28.8 | 28.0 | |
| Stage 4 | 69.5 | 64.7 | | 67.6 | 66.8 | |
| *WIfI W grade* | | | .091 | | | .86 |
| Grade 1 | 38.0 | 44.5 | | 41.1 | 41.1 | |
| Grade 2 | 43.5 | 45.7 | | 42.4 | 45.9 | |
| Grade 3 | 18.5 | 9.8 | | 16.5 | 13.0 | |
| *WIfI I grade* | | | .17 | | | .82 |
| Grade 2 | 17.4 | 24.4 | | 23.5 | 22.1 | |
| Grade 3 | 82.6 | 75.6 | | 76.5 | 77.9 | |
| *WIfI fI grade* | | | .37 | | | .99 |
| Grade 0 | 15.8 | 17.7 | | 15.6 | 17.2 | |
| Grade 1 | 28.5 | 30.9 | | 32.8 | 29.2 | |
| Grade 2 | 49.5 | 48.2 | | 46.5 | 49.5 | |
| Grade 3 | 6.3 | 3.2 | | 5.2 | 4.0 | |
| *Femoropopliteal endovascular procedure* | 36.0 | 37.2 | .77 | 40.0 | 37.2 | .66 |
| Stent implantation | 15.7 | 17.7 | .82 | 20.7 | 17.6 | .59 |
| Drug technology | 14.7 | 13.8 | .57 | 14.0 | 14.1 | .96 |

Data are presented as median (interquartile range) or %. Data are estimates after multiple imputation. IPTW = inverse probability of treatment weighting; IFW = in line flow to the wound; WIfI = Wound, Ischaemia, and foot Infection.

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**Table 3.** Incidence of clinical outcomes in patients with and without in line flow to the wound (IFW) after inverse probability of treatment weighting.

| Event | Incidence in non-IFW group (per 100 person years) | Incidence in IFW group (per 100 person years) | Incidence risk ratio |
|---|---|---|---|
| Wound healing | 16.1 (8.5 – 30.5) | 34.5 (23.7 – 50.2) | 2.13 (1.08 – 4.20) ($p$ = .030) |
| Death | 21.7 (15.5 – 30.3) | 16.1 (12.5 – 20.7) | 0.74 (0.48 – 1.16) ($p$ = .18) |

Data are estimates (95% confidence interval) after multiple imputation. IFW = in line flow to the wound.

was comparable between those with and without direct revascularisation in the non-IFW group, with an incidence risk ratio of 0.68 (95% CI 0.14 – 3.39; $p$ = .63). There was no statistically significant interaction effect between IFW and direct revascularisation for wound healing ($p$ for interaction = .51).

## DISCUSSION

In the treatment of CLTI with ischaemic wounds, revascularisation is crucial for wound healing and limb salvage.[1,2,4] Traditionally, the goal of revascularisation was to establish

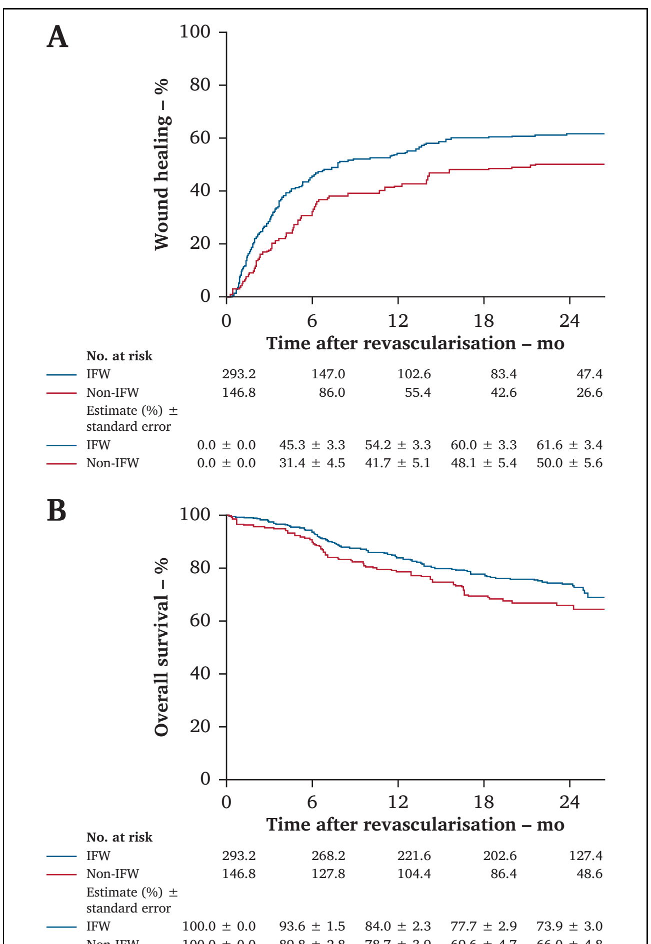


**Figure 3.** Cumulative Kaplan–Meier estimate of (A) wound healing rate and (B) overall survival after inverse probability of treatment weighting (IPTW). Data are estimates after multiple imputation. IFW = in line flow to the wound.

in line flow to the foot.[2,4] However, despite its establishment, a substantial proportion of patients failed to heal ischaemic wounds, which was attributed to inadequate vascular connections between the revascularised tibial artery and the pedal ischaemic area.[8,9] Subsequently, the concept of the angiosome was introduced, which was originally derived from anatomical studies in plastic reconstructive surgery.[8] The angiosome concept in the field of vascular intervention was based on the principle that ischaemic wound areas have a one to one link with their respective supplying tibial arteries. Some retrospective studies supported the usefulness of angiosome guided revascularisation for the improvement of clinical outcomes, while others refuted it.[10–13] A major limitation of the angiosome concept would be that the angiosome was conceptualised based on the anatomical findings of cadavers without atherosclerotic disease, and individual anatomical variations, variant circulation patterns, and collateral circulation were not taken into consideration. Revascularisation of a tibial artery would not always guarantee perfusion of the corresponding angiosome in patients with atherosclerotic lower extremity arterial disease. Recent studies suggested the importance of collateral circulation and inframalleolar arteries in achieving successful wound healing.[14–17] The present study, using core laboratory assessment, supports their importance in IP revascularisation.

Patients with WIfI clinical stage 4 and those with advanced age, diabetes mellitus, and on dialysis, often presenting with IP arterial disease, are typically precluded from clinical trials.[18,19] One strength of the present study was that these patients were included. Another strength was that ischaemic wounds and in line flow were assessed by a core laboratory. The present study showed a higher wound healing rate in cases successfully establishing IFW than those without IFW, supporting the shift of the revascularisation goal of in line flow to the foot to IFW. The subsequent interaction analysis revealed that the association between IFW and wound healing was not statistically significantly different between the bypass and endovascular procedure groups, suggesting that establishing IFW would be important in both revascularisation strategies. Furthermore, in cases establishing IFW, the wound healing rate was not statistically significantly different between direct and indirect revascularisation based on the classical angiosome concept. This finding is consistent with previous studies[15,16] which reported that indirect revascularisation with a good

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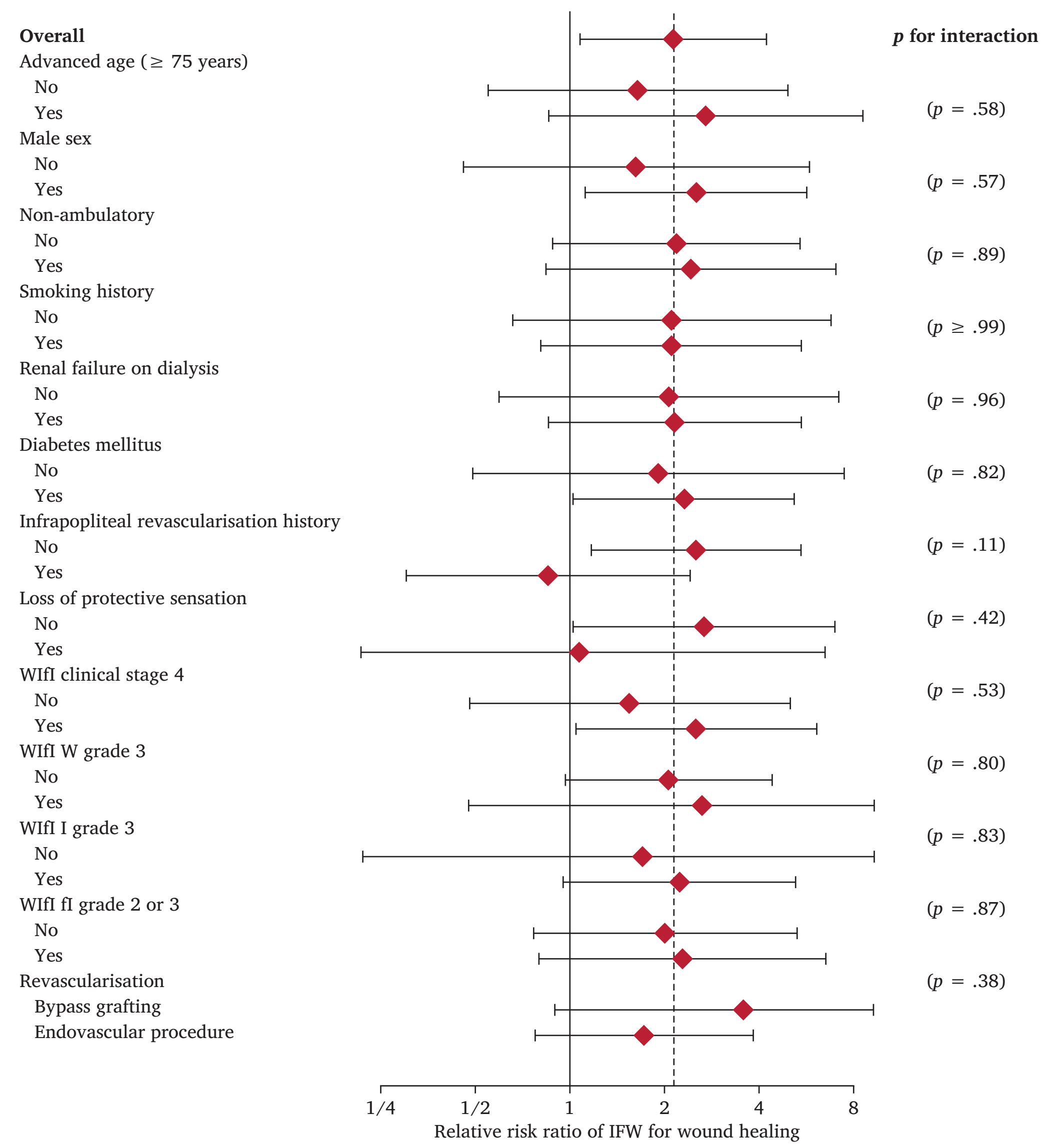


**Figure 4.** Interaction effect of baseline characteristics on the association between in line flow to the wound (IFW) and wound healing after inverse probability of treatment weighting (IPTW). Data are estimates after multiple imputation. Error bars indicate 95% confidence intervals. WIfI = Wound, Ischaemia, and foot Infection.

collateral artery, corresponding to revascularisation establishing IFW but not meeting the criteria for direct revascularisation, had a similarly beneficial impact on wound healing and limb salvage compared with direct revascularisation with a good outflow in patients with CLTI with tissue loss. Collateral vessels of the IP artery are a crucial safety conduit, enabling one tibial artery to provide blood flow for an adjacent angiosome when the source artery of the adjacent angiosome is occluded.[15,16] Collateral vessels substantially influence the distribution of arterial flow in the foot, saving the limb from ischaemia. IP arterial disease progresses gradually and collateral vessels are typically developed before the source artery is completely occluded. The present findings suggest that establishing direct perfusion to wounds would be important for wound healing. Successful in line vascular alignment to wounds would be crucial, irrespective of whether it involves direct revascularisation or indirect revascularisation with collateral circulation. The classic angiosome concept would not accurately capture the correlation between wounds and arteries. Peripheral tissue perfusion would be determined by IFW, rather than the tibial arterial blood flow to the foot. Angiographic findings in individual patients, rather than schematic angiosome mapping, would serve for decision making to achieve wound healing.

### Study limitations

Firstly, the current study was not a randomised trial. However, propensity score analysis was adopted to minimise the differences in baseline characteristics. Secondly, the present results were shown in Japanese patients with CLTI who were more likely to have poorer comorbidities. The results require validation in other ethnic groups. Thirdly, the sample size was relatively small and it was not possible to analyse intergroup difference in subsets of the study population. Fourthly, details of anatomical variants were not assessed. Finally, data on the reason why physicians determined the target artery for revascularisation were not collected.

## Conclusion

The current study revealed that IP revascularisation establishing IFW was significantly associated with a higher wound healing rate, while classical angiosome guided revascularisation was not.

## ETHICAL STATEMENT

This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the participating centres. Informed consent was obtained from the participants or, if not possible, from their family.

## CONFLICTS OF INTEREST

None.

## FUNDING

The WARRIORS study was sponsored by Japan Endovascular Treatment Conference (JET), M-TOWER 11F, 1-7-5 Momochihama, Sawara-ku, Fukuoka 814-0001, Japan. The funding bodies played no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

## ACKNOWLEDGEMENTS

The authors thank the staff of EndoCore and the secretary of the Japan Endovascular Treatment Conference, as well as the cardiac catheterisation laboratory medical staff and clinical research coordinators in the participating centres.

## APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2024.07.024.

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