Received: 8 July 2023 | Accepted: 10 July 2023

DOI: 10.1002/dmrr.3700

RESEARCH ARTICLE

WILEY

Effectiveness of revascularisation for the ulcerated foot in patients with diabetes and peripheral artery disease: A systematic review

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Abbreviations: CLTI, chronic limb threatening ischaemia; Cochrane RoB 2, Cochrane risk-of bias tool for randomised trials; CTA, computed tomography angiography; DFU, diabetes-related foot ulcer; DR, direct revascularisation; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; IR, indirect revascularisation; IRc, indirect revascularisation with collaterals; IWGDF, International Working Group on the Diabetic Foot; MALE, major adverse limb event; NOS, Newcastle-Ottawa Scale; PAD, peripheral artery disease; PICO, population, intervention, comparison, outcome.

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Abstract

Introduction: Peripheral artery disease (PAD) is associated with an increased likelihood of delayed or non-healing of a diabetes-related foot ulcer, gangrene, and amputation. The selection of the most effective surgical technique for revascularisation of the lower limb in this population is challenging and there is a lack of conclusive evidence to support the choice of intervention. This systematic review aimed to determine, in people with diabetes and tissue loss, if direct revascularisation is superior to indirect revascularisation and if endovascular revascularisation is superior to open revascularisation for the outcomes of wound healing, minor or major amputation, and adverse events including mortality.

Methods: Title and abstract searches of Medline, Embase, PubMed, and EBSCO were conducted from 1980 to 30th November 2022. Cohort and case-control studies and randomised controlled trials reporting comparative outcomes of direct (angiosome) revascularisation (DR) and indirect revascularisation (IR) or the comparative outcomes of endovascular revascularisation and open or hybrid revascularisation for the outcomes of healing, minor amputation, and major amputation in people with diabetes, PAD and tissue loss (including foot ulcer and/or gangrene) were eligible. Methodological quality was assessed using the Cochrane risk-of-bias tool for randomised trials, the ROBINS-I tool for non-randomised studies, and Newcastle-Ottawa Scale for observational and cohort studies where details regarding the allocation to intervention groups were not provided.

Results: From a total 7086 abstracts retrieved, 26 studies met the inclusion criteria for the comparison of direct angiosome revascularisation (DR) and indirect revascularisation (IR), and 11 studies met the inclusion criteria for the comparison of endovascular and open revascularisation. One study was included in both comparisons. Of the included studies, 35 were observational (31 retrospective and 4 prospective cohorts) and 1 was a randomised controlled trial. Cohort study quality was variable and generally low, with common sources of bias related to heterogeneous participant populations and interventions and lack of reporting of or adjusting for confounding factors. The randomised controlled trial had a low risk of bias. For studies of DR and IR, results were variable, and it is uncertain if one technique is superior to the other for healing, prevention of minor or major amputation, or mortality. However, the majority of studies reported that a greater proportion of participants receiving DR healed compared with IR, and that IR with collaterals may have similar outcomes to DR for wound healing. For patients with diabetes, infrainguinal PAD, and an adequate great saphenous vein available for use as a bypass conduit who were deemed suitable for either surgical procedure, an open revascularisation first approach was superior to endovascular therapy to prevent a major adverse limb event or death (Hazard Ratio: 0.72; 95% CI 0.61–0.86). For other studies of open and endovascular approaches, there was generally no difference in outcomes between the interventions.

Conclusions: The majority of available evidence for the effectiveness of DR and IR and open and endovascular revascularisation for wound healing and prevention of minor and major amputation and adverse events including mortality in people with diabetes, PAD and tissue loss is inconclusive, and the certainty of evidence is very

low. Data from one high quality randomised controlled trial supports the use of open over endovascular revascularisation to prevent a major limb event and death in people with diabetes, infrainguinal disease and tissue loss who have an adequate great saphenous vein available and who are deemed suitable for either approach.

KEYWORDS
diabetes, diabetic foot, endovascular treatment, foot ulcer, peripheral artery disease, revascularisation

1 | INTRODUCTION

Peripheral artery disease (PAD) affects up to 50% of patients with a diabetes-related foot ulcer (DFU), and its presence is associated with increased likelihood of delayed or non-healing of DFU, gangrene, and amputation in addition to elevated rates of cardiovascular morbidity and mortality.[1] However, multiple factors may contribute to delayed or non-healing of DFU, including the presence of infection, wound size and depth, elevated pressure at the wound site and inadequate wound care.[2] Even in the presence of PAD, there is observational evidence of DFU healing occurring within 12 months in up to half of the people deemed unsuitable for revascularisation due to technical contraindication or surgical risk posed by co-morbidities.[3,4] High rates of post-intervention delayed healing, infection, and increased risk of more proximal amputation after minor amputation as well as non-healing after technically successful revascularisation procedures have also been documented in people with DFU.[5,6] However, in the presence of chronic limb threatening ischaemia (CLTI) or where there is a lack of progress in wound healing despite best care practices, revascularisation may be required and if so, should be prioritised. This is supported by observational research demonstrating that a shorter time from ulcer development to revascularisation (<8 weeks) is associated with a higher probability of DFU healing and lower likelihood of limb loss.[4]

The selection of the most effective surgical technique for revascularisation is challenging as there is a lack of conclusive evidence to support the choice of revascularisation technique in people with PAD and DFU or tissue loss. Angiosome-based revascularisation, where blood flow is restored directly to the artery supplying the site of tissue loss, is proposed to improve outcomes in the presence of severe ischaemia.[7] An angiosome, is within this context defined as a three-dimensional unit of deep tissue and overlying skin fed by a source artery, which in the foot can be the posterior or anterior tibial artery or the peroneal artery. Direct revascularisation (DR) involves revascularisation of the tibial artery supplying the angiosome in which the tissue loss has occurred (Figure 1). The alternative to this is indirect revascularisation (IR), where the treated tibial artery is the artery in which successful in-line flow to the foot is most likely to be achieved by endovascular techniques or the artery deemed to be the best tibial outflow vessel for anastomosis in bypass surgery but does not directly supply the affected area of tissue loss. Several studies have also described indirect revascularisation with collaterals (IRc) to describe revascularisation of an artery which has well-defined collaterals into the angiosome where tissue loss has occurred.[8–11] However, the effectiveness of DR for wound healing and prevention of amputation in the management of diabetes-related foot complications remains controversial.[12–14] The effect of pedal disease and the loss of pedal arch patency in people with diabetes is likely to

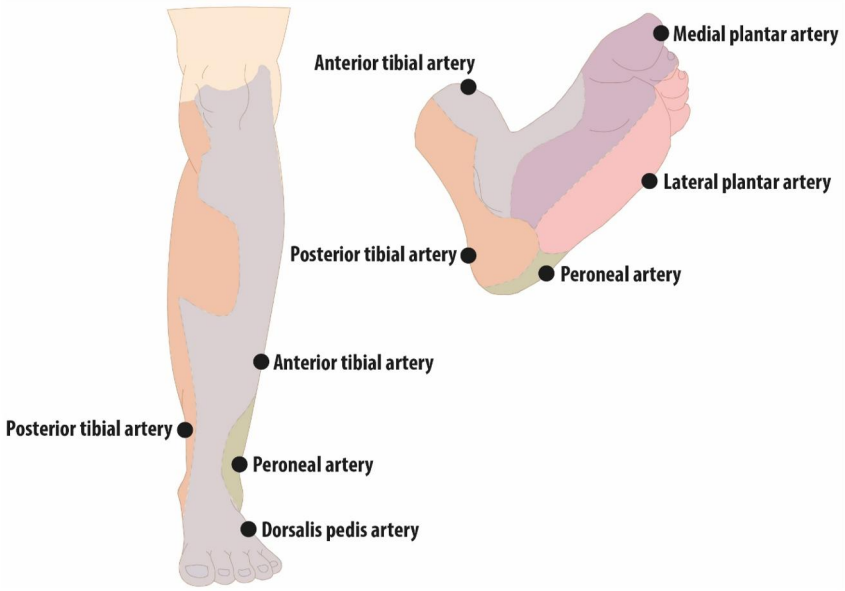

FIGURE 1 Angiosome distribution in the lower leg and foot.

complicate the outcomes of angiosome-based revascularisation.[14] The success of DR may also be complicated by dual angiosomal supply to affected wounds (for example, where there is a large wound or presence of multiple wounds supplied by difference angiosomes) and challenges with the classification of angiosomes.[15,16] Similarly, for IR, the influence of the presence or absence of well-defined collaterals that are frequently not separately identified in analyses is likely to affect outcomes.[17]

Revascularisation by open surgical or endovascular procedures in people with diabetes and PAD is often also technically difficult due to the high frequency of multi-segmental disease, more distally distributed disease pattern, impaired collateral formation, long segment tibial artery occlusions and high prevalence of medial arterial calcification.[18–20] Even in the general population, studies in people with CLTI have failed to conclusively establish the benefit of one technique over the other for outcomes of wound healing, mortality and amputation-free survival.[21,22]

The aim of this systematic review was to determine, in people with diabetes and tissue loss, if DR is superior to IR for wound healing or to prevent minor and major amputation and adverse events including mortality, and, if endovascular revascularisation is superior to open revascularisation for wound healing, or to prevent minor and major amputation and adverse events including mortality. This systematic review forms the basis for developing the intersocietal International Working Group on the Diabetic Foot (IWGDF), European Society for Vascular Surgery, Society for Vascular Surgery guidelines on peripheral artery disease in people with diabetes mellitus and a foot ulcer and updates the previous systematic review.[23]

2 | METHODS

2.1 | PICO development

First, the population of interest (P), interventions (I), and outcomes (O) were defined, and clinical questions were formulated accordingly by the assessors (i.e., the authors of this paper). Methods for this are detailed in Supplementary File S1. The PICOs that were developed are listed below.

2.1.1 | PICO

In a person with diabetes, PAD, and tissue loss (including a foot ulcer or gangrene), is direct angiosome revascularisation superior to indirect revascularisation to heal a foot ulcer or prevent amputation (minor/major) and mortality and other adverse events.

2.1.2 | PIC

In a person with diabetes, PAD, and tissue loss (including a foot ulcer or gangrene), is endovascular revascularisation superior to open or hybrid revascularisation to heal a foot ulcer or prevent amputation (minor/major) and mortality and other adverse events.

2.2 | Search methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement with content verified using the AMSTAR tool (PROSPERO ID: CRD4202340152). Title and abstract searches of Medline, Embase, PubMed, and EBSCO were conducted from 1980 to 30th November 2022. Due to the alteration of this review from the previous iteration to restrict studies to comparison of interventions, new search strings were used and records were searched again from the original start date of 1980. The search strings for both databases are provided in Supplementary File S1. A set of 10 key publications was used to validate the search string. A protocol has not been published separately.

2.3 | Inclusion/exclusion criteria

To be eligible for inclusion, a study was required to report the comparative outcomes of DR and IR or the comparative outcomes of endovascular revascularisation and open or hybrid revascularisation. The study population was required to have diagnosed PAD, >80% of participants with tissue loss, include at least 40 patients with >80% of the population diagnosed with diabetes or where the results of at least 30 patients with diabetes were reported separately, and report on primary outcomes including ulcer healing, minor amputation, major amputation and adverse events including mortality/survival.

Studies reporting only on aorto-iliac disease were excluded as the treatment of supra-inguinal disease is similar in patients with or without diabetes.[24] Studies were excluded if they reported only on medical, pharmacological, or topical therapies or if they compared different revascularisation technologies.

2.4 | Primary outcome measures and definitions

The primary outcome measures of interest included DFU healing, minor amputation, major amputation, mortality, post-operative complications and reinterventions (as defined by individual studies). Studies reporting relevant composite primary outcomes as defined by individual studies (e.g. major adverse limb event [MALE]) were also included.

For the purpose of this systematic review, *peripheral artery disease* (PAD): was defined as obstructive atherosclerotic vascular disease of the arteries from the aorta to the foot with clinical symptoms, signs, or abnormalities on non-invasive or invasive vascular assessment, resulting in disturbed or impaired circulation in one or more

extremities. We accepted the diagnosis of *diabetes mellitus* as it was made according to the individual publication. *Tissue loss* was defined as any lesion of the skin breaching the epithelium or the presence of ulceration or gangrene.

2.5 | Data collection and analysis

Two reviewers (Vivienne Chuter and Robert Fitridge or Nicolaas Schaper) independently screened the abstracts for inclusion, and a third reviewer (Robert Fitridge or Nicolaas Schaper) adjudicated any conflicts. Full-text articles of included abstracts were retrieved and assessed for inclusion independently by the same two reviewers (except where conflict of interest for publications a reviewer was an author of, in which case the third reviewer was used) with the same third reviewer used to adjudicate conflicts where required. Where the third reviewer also had a conflict another reviewer was to be sought from the author group, however this was not required. Hand searching of the reference list of appropriate articles was also conducted. Data extraction was performed by Vivienne Chuter or Nicolaas Schaper and cross-checked by Nicolaas Schaper or Robert Fitridge using a customised extraction form. For open and endovascular surgery outcomes, no distinction was made amongst various endovascular techniques (e.g., angioplasty, stenting, subintimal angioplasty, atherectomy), which were all referred to as endovascular therapy. Similarly, methods of open revascularisation were not differentiated.

Analysis of outcome data for DR, IR and IRc (when reported) and endovascular and open revascularisation was conducted descriptively. Previous meta-analysis for DR and IR has demonstrated excessive heterogeneity in a similar data set for the primary outcome of healing.[25] Variable reporting of IR and IRc, lack of randomisation of participants into interventions of both studies of IR and DR and studies of endovascular and open revascularisation, and the retrospective nature of the majority of available evidence for all these interventions were considered by the authors of this review to preclude pooled analyses of available data.

2.6 | Quality assessment

The risk of bias was assessed according to the type of study identified. For randomised controlled trials, the Cochrane risk-of-bias tool for randomised trials (RoB 2) was used.[26] This tool assesses six domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, and selective outcome reporting. The ROBINS-I tool was utilised for non-randomised studies that compared the health effects of two or more interventions where intervention groups were allocated during the course of usual treatment decisions and allocation details were provided or where the described method of allocation falls short of full randomisation.[27] Seven distinct domains through which bias might be introduced are judged (confounding factors, selection of participants into the study, classification of interventions, deviations from intended intervention, missing data, measurement of outcomes, and selection of the reported results). Studies received an overall judgement of low, moderate, serious, critical, and no information risk of bias. For non-randomised studies, including observational and cohort studies where details regarding the allocation to intervention groups were not provided, the Newcastle-Ottawa Scale (NOS) was employed to assess the risk of bias.[28] The NOS is a star scoring system comprising three domains (selection of study groups, comparability of the groups; and ascertainment of the outcome) containing eight items. All domain items can be assigned a maximum of one star except comparability, which can be assigned two stars. A total score (maximum 9) is generated by the sum of the stars awarded. Studies were classified as having low (≤5 stars), moderate (6 or 7 stars), or high quality (8 or 9 stars). Two reviewers (Vivienne Chuter and Robert Fitridge) independently assessed the quality of the studies with disagreement to be resolved by a third reviewer (Nicolaas Schaper) however this was not required. There was no minimum level of quality required for inclusion in this review.

2.7 | Evidence statements

Two investigators (Vivienne Chuter and Robert Fitridge) drew conclusions for each intervention based on the strength of the available evidence, formulated as evidence statements, and accompanying assessment of the quality of the evidence, according to GRADE. The authors rated the certainty of the evidence for each formulated evidence statement as 'high', 'moderate', 'low', or 'very low' in relation to the strength of confidence in estimates of the effect.[29] GRADE defines 'high' as 'We are very confident that the true effect lies close to that of the estimate of the effect'; 'moderate' as 'We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different'; 'low' as 'Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect', and 'very low' as 'We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect'.[29] The rating was determined based on the study design, the risk of bias, (in)consistency of results, (im)precision, (in)directness, publication bias, effect size and evidence of dose-response relation.[30] Each evidence statement was phrased in accordance with the methods described by GRADE. When the certainty of evidence was rated as moderate, the evidence statement was generated using the words 'likely results in …'; likewise, when rated with a low certainty of effect, the statement contained 'may result in …'; for evidence rated as having a very low certainty of effect, the statement contained '(very) uncertain'. All authors discussed these evidence statements until consensus was reached.

3 | RESULTS

3.1 | Search results

From a total 7086 abstracts retrieved, 26 studies met the inclusion criteria for the comparison of DR and IR and 11 studies met the inclusion criteria for the comparison of endovascular and open revascularisation (Figure 2, Supplementary Tables S1 and S2).

3.2 | Direct angiosome and indirect revascularisation

3.2.1 | Characteristics of included studies

The 26 studies comparing DR and IR included 5190 people with diabetes. Of these, 3107 participants were identified as having DR and 2150 were identified as having IR. Four studies differentiated between outcomes for those receiving IR and those receiving IRc[9–11,31] and 1 study conducted a sub-analysis of wound healing and limb salvage outcomes for IR and IRc interventions.[32] Twenty-two studies were retrospective cohort studies[8,10,11,13,32–49] and 4 were prospective cohort studies.[9,31,50,51] One study described an 'angiosome' model (DR) compared to a 'non-angiosome'(IR) model of revascularisation,[33] 3 studies compared outcomes of DR and IR for multiple procedures (e.g. endovascular and open),[47,48,50] 4 studies compared DR and IR for open revascularisation[13,32,43,52] and 20 studies compared outcomes of DR and IR (±IRc) for endovascular procedures.[8–11,31,32,34–42,44,46,49–51] Follow-up time was variable between studies, but all had a reported a follow-up time of at least 6 months. Data from the 12-month time point were used where available for study outcome comparison. Reporting of other adverse events was limited and included clinical success, freedom from intervention, reintervention and restenosis (Supplementary Table S1).

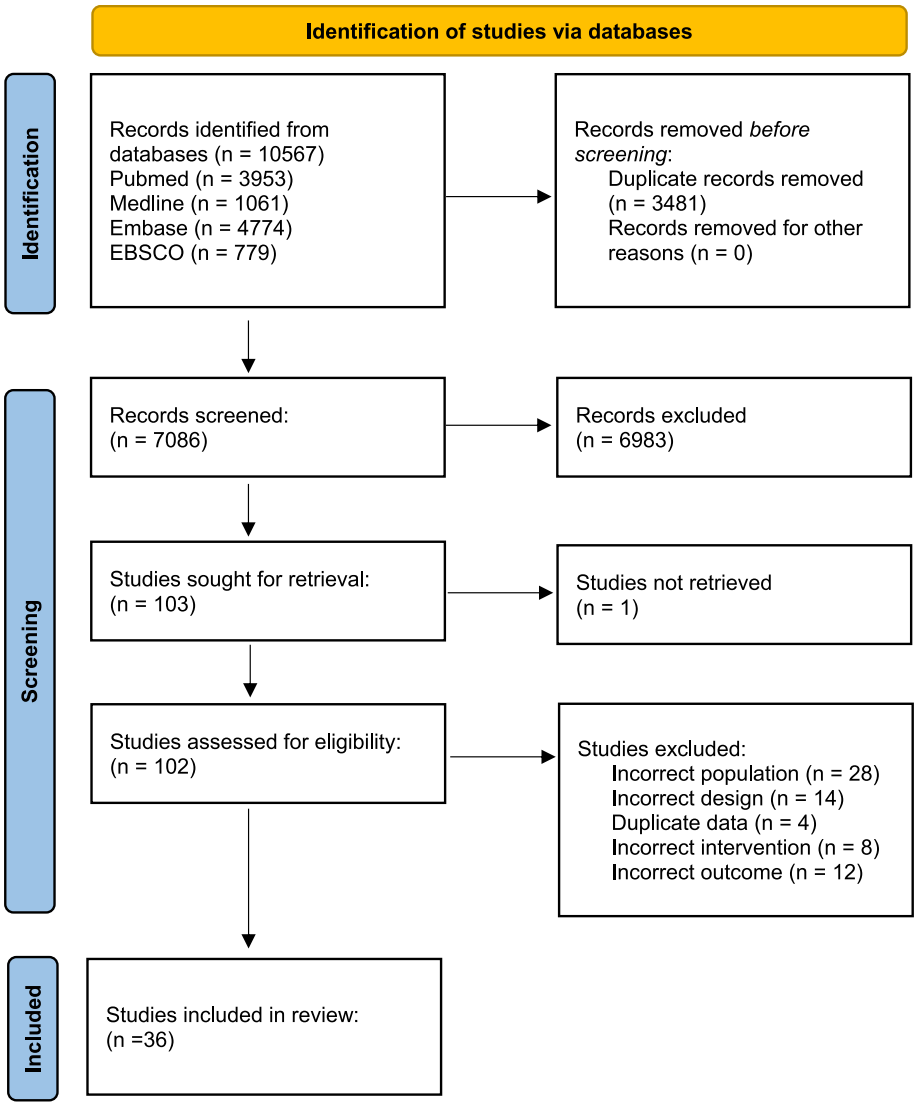

FIGURE 2 Preferred Reporting Items for Systematic Review and Meta-Analysis flow diagram.

3.2.2 | Methodological quality and certainty of evidence

No included studies were randomised controlled trials or met the ROBINS-I criteria for non-randomised trials. All studies were therefore assessed with the NOS. Four studies were assessed as being of moderate quality[13,36,40,46] and the remainder were of low quality and at high risk of bias (Table 1). Sources of bias related to the retrospective nature of the majority of studies, the heterogeneity between participant populations and the severity of the foot lesion (extent of tissue loss, severity of ischaemia, presence of sepsis), and the presence of pre-intervention prognostic factors including co-morbidities

TABLE 1 Summary table of results from Newcastle-Ottawa bias analysis of non-randomised studies.

Article	Selection	Comparability	Outcome	Total score	Type
Acin (2014)	**		***	5	Retrospective
Alexandrescu (2008)	*		**	3	Retrospective
Alexandrescu (2011)	*		*	2	Retrospective
Alexandrescu (2020)	**	**	***	7	Prospective
Ambler (2017)	***	*	***	7	Retrospective
Augusto (2019)	*		*	2	Retrospective
Azuma (2012)	**	**	**	6	Retrospective
Bekeny (2021)	*8		**	4	Retrospective
Cheun (2020)	**	**	**	6	Retrospective
Cury (2019)	**	*	**	6	Retrospective
Darling (2018)	***	**	***	7	Retrospective
de Athayde Soares (2021)	**		**	4	Retrospective
Deery (2022)	***		**	5	Retrospective
Del Carmen (2021)	**		**	4	Retrospective
Fossaceca (2013)	**		***	5	Retrospective
Gomez-Sanchez (2022)	**		**	4	Retrospective
Grey (2020)	***	*	**	6	Retrospective
Hicks (2016)	**	*	**	5	Retrospective
Huo (2022)	**		*	3	Retrospective
Iacopi (2021)	**	*	***	6	Retrospective
Jeon (2016)	**		**	4	Retrospective
Ji (2018)	**		**	4	Retrospective
Kabra (2013)	**		**	4	Prospective
Khalefa (2019)	**		***	5	Prospective
Kreider (2020)	*		*	2	Prospective
Lejay (2014)	*		*	2	Retrospective
Lo (2018)	**		*	3	Retrospective
Mohapatra (2018)	***		**	5	Retrospective
Söderström (2013)	**	**	**	6	Retrospective
Špillerová (2017)	***		**	5	Retrospective
Troisi (2017)	**		**	4	Retrospective
Weaver (2018)	**		**	4	Retrospective
Wölfle (2000)	**		***	5	Retrospective
Zhan (2012)	**		**	4	Retrospective
Zheng (2016)	***		**	5	Retrospective

for example, renal disease. Baseline variables such as foot staging (e.g., by the SVS Wound Ischaemia, foot Infection classification system [WIfI]) and extent of tissue loss were infrequently reported. Lack of reporting or adjusting for confounding factors (both social and biomedical) with only two studies using propensity score matching, and lack of statistical analysis of the outcomes also affected most studies. There was incomplete reporting of interventions with the majority of studies not differentiating between IR and IRc. Results for all outcomes were inconsistent between studies with variation outcomes across categories of revascularisation procedures (e.g., endovascular or open), which included a range of interventions reducing study comparability. The certainty of evidence was therefore rated as very low for all outcomes.

3.2.3 | Outcomes

Healing

One study comparing DR to IR approaches demonstrated higher rates of wound healing for both 3 and 1 or 2 patent vessels with the DR approach (wound healing at 12 months: 3 patent vessels IR: 56.5%, DR:79%, 1 or 2 patent vessels: IR: 52.8%, DR: 79.2%). For studies of multiple procedures (open and bypass), all studies reported a greater proportion of participants healed with a DR (66.9%–96.4%) compared to IR (54.6%–85.7%).[47,48,50] For open revascularisation procedures, the proportion of participants who healed was consistently higher in the DR groups after 12 months of follow-up (DR: 81%–90.9%, IR: 41%–68.5%).[32,43,45]

Thirteen studies evaluating healing following endovascular intervention with DR and IR approaches reported a higher proportion of participants healing with a DR approach at 6-[31] and 12 months follow-ups.[8–10,35,36,38–42,46,51] In addition, 1 study reported that the proportion of participants who had not healed was greater for those receiving IR (DR: 26.6%, IR:90%).[11] One study reported no difference in wound healing between DR and IR[34] and 2 studies reported a greater proportion of participants who received IR healing compared to those who received DR.[32,37]

Five studies evaluating healing outcomes reported IR and IRc separately.[8–11,31] Of those, three studies reported a greater proportion of participants in the IRc group healed compared to the DR group.[8,10,31] For the remaining studies, IRc was associated with higher proportions of participants healing compared to IR[9] and lower proportion of people who had *not* healed at 12 months (DR: 26.6%, IRc: 31.1% IR: 90%).[11] One study compared time to healing by Cox proportional hazards analysis in a sub-analysis of IRc or IR and found that IRc did not significantly affect wound healing outcomes (hazard ratio not reported, $p = 0.245$).[32]

Amputation and amputation-free survival

Two studies of participants undergoing IR or DR with an endovascular approach reported minor amputation outcomes.[38,51] Of these, one study demonstrated a smaller proportion of participants required minor amputation following DR than IR (DR: 33.5% IR: 61.7%),[38] and one study showed no difference in the requirement for minor amputation between the two groups (DR and IR both 50%).[51]

Major amputation, (unspecified) amputation and limb loss were reported in nine studies.[10,33,38–41,45,48,51] Four studies reported outcomes of major amputation in relation to endovascular procedures.[10,38,39,51] Three of the 4 studies reported proportionally fewer major amputations in those undergoing DR with percentage of study population affected by major amputation ranging from 2.9% to 13.4% for DR and 9.2% to 27.2% for IR.[10,39,51] One study reported a similar rate of major amputation for DR and IR (DR:9.6%, IR 8.8%).[38]

One study comparing a DR approach to an IR approach demonstrated that the proportion of people amputation-free at 12 months was higher in the DR group (DR: 90%, IR: 84%).[33] Another study of multiple procedures reported a higher proportion of people suffering limb loss in those receiving IR (Limb loss at 12 months: DR 12%, IR 33.4%).[48] This finding was consistent with a small study of open revascularisation where the proportion of participants who had undergone amputation at 12 months was much lower for those receiving DR (Amputation: DR:9.1%, IR: 38.1%).[45]

Two studies investigating outcomes of IR and DR for endovascular procedures reported rates of MALE at 6[9] and 12 months.[8] In both studies, a greater percentage of participants undergoing DR was MALE free at 6 and 12 months than those receiving IR. In addition, IRc also resulted in lower rates of MALE compared to IR in both studies.[8,9]

Amputation-free survival was evaluated in 1 study of open revascularisation[32] and 8 studies of endovascular surgery.[9,10,32,34,37,39,46,49] For open revascularisation, amputation-free survival at 12 months was highest for those undergoing IR (IR: 42.2%, DR: 37.3%).[32] For endovascular procedures amputation-free survival was variable. Better outcomes for DR in relation to amputation-free survival were also reported in 5 studies.[8,9,13,39,46] In contrast, 1 study reported no significant difference between the DR and IR groups for amputation-free survival at 24 months[37] and an additional study found minor amputation-free survival at 12 months was higher for IR than DR.[49] Of note, 3 studies separated IR and IRc and all reported that, after follow-up of 6–24 months, IRc was associated with a higher rate of amputation-free survival than IR.[8–10] Moreover, in 2 of these studies, IRc was associated with a higher percentage of amputation-free survival also compared to DR (DR: 67.5% IRc: 73.3% IR: 61.9%,[8] DR:85.7% IRc: 89.5% IR: 69.7%[10]).

Limb salvage

Seventeen studies reported limb salvage outcomes including 1 study investigating DR and IR approaches,[33] 1 study in a population undergoing multiple procedures,[50] 3 studies in participants undergoing open revascularisation[13,32,43] and 13 studies in people receiving endovascular procedures.[8,11,32,34,35,37,38,41,42,44,46,49,51] Limb salvage rates at 12 months were higher for participants receiving DR for both 3 patent vessels (DR: 95.3% and IR: 82.3%) and ≤2 patent vessels (DR: 95.3%,IR: 82.3%).[33] In participants undergoing open revascularisation all studies reported an equivalent or higher percentage of limb salvage associated with DR (ranging from 20.1% to 100%) than

IR (ranging from 18% to 100%) at 12-month follow-up.[13,32,43] Another study[13] also reported data for propensity matched pairs (96 limbs) at 24 months with DR having a higher percentage of limb salvage (DR: 97.8% IR: 92.3%).

Of the 13 studies of limb salvage outcomes for endovascular procedures[8,11,32,34,35,37,38,41,42,44,46,49,51] 6 studies reported higher rates of limb salvage in those undergoing DR at follow-up between 12 and 24 months.[8,11,35,42,46,51] In one additional study[44], IR was found to be an independent predictor of failure of endovascular limb salvage (OR 2.03, $p = 0.02$). Two studies[34,37] reported no statistically significant difference between groups. Four studies reported slightly higher limb salvage at 12 months for IR (IR 32.8%–100% DR: 20.3%–96.8%).[32,38,41,49] Two studies reported limb salvage outcomes for IR and IRc, with IRc having similar outcomes compared to DR in both studies at 12 months[11] and 24 months[8] (12 months: DR: 91.2% IRc: 86.7% IR: 70.0%, 24 months: DR: 88.9% IRc: 84.8% IR: 59.0%). This was consistent with a sub-analysis conducted in 1 study[32] that demonstrated at 1 year follow-up a significantly worse limb salvage rate for IR compared to IRc (hazard ratio 0.45, 95% CI 0.25–0.814, $p < 0$ 0.008).

Mortality and survival

Four studies reported the outcome of mortality.[45,48,50,51] Two studies of participants undergoing multiple procedures reported lower mortality in those undergoing DR (DR 0%–10.3%, IR 11.2%–20%).[48,50] One small study[45] in participants undergoing surgical revascularisation reported a statistically non-significant difference in mortality between DR and IR (DR: 13.6%, IR: 28.6%). One study[51] reported a non-significant difference in 12-month mortality for DR and IR in those undergoing endovascular procedures (DR:10%, IR:15.4%).

Survival was reported in 9 studies with a follow-up between 12 and 24 months.[8,9,33,34,37,39,43,46,49] Five studies reported no or little difference between IR and DR for survival for DR and IR approaches[33] and endovascular procedures.[32,34,37,46] Two studies reported higher rates of survival at 12 months occurring in those undergoing endovascular procedures with DR (DR: 83.3%–90.1% IR: 53.7%–66.6%). A further 2 studies evaluated survival outcomes for open revascularisation with opposing results.[32,43] One study[43] reported higher 12-month survival for participants undergoing DR than IR (DR 78%, IR 65%). In contrast, another study[32] reported lower survival with the same procedure (DR: 21.3%, IR: 32.3%).

3.2.4 | Evidence statements

In people with diabetes, PAD and a foot ulcer, it is uncertain if direct revascularisation is superior to indirect revascularisation to heal a foot ulcer or prevent minor or major amputation.[8–11,13,37–41,46,51]

Certainty of evidence: very low.

In people with diabetes, PAD and a foot ulcer, it is uncertain if direct revascularisation is superior to indirect revascularisation to prevent mortality or increase survival.[8,9,33,34,37,39,43,45,46,48–51]

Certainty of evidence: very low.

3.3 | Endovascular and open revascularisation

3.3.1 | Characteristics of included studies

The 11 studies comparing endovascular and open procedures included 28,182 participants who underwent an endovascular procedure and 9515 who underwent an open procedure (Supplementary Table S2).[44,53–62] One study reported the inclusion of hybrid procedures affecting 4.9% of participants undergoing open revascularisation. Ten of the studies were retrospective cohort studies,[44,53–55,57–62] and one was a randomised controlled trial[56] which reported a sub-analysis of participants with diabetes. The retrospective studies reported on infrapopliteal interventions,[53] first-time revascularisation graft and first percutaneous transluminal angioplasty in participants with CLTI,[54] open revascularisation or peripheral vascular intervention (undefined) for tissue loss,[55] endovascular or open revascularisation in CLTI participants requiring transmetatarsal amputation,[57] endovascular and open revascularisation for limb salvage in people with diabetes, endovascular and open infrageniculate revascularisation for rest pain or tissue loss,[59] endovascular and open revascularisation in people with DFU undergoing diabetic limb salvage,[44] endovascular (percutaneous transluminal angioplasty) and open revascularisation in people with tibial arterial disease and ischaemic tissue loss,[62] endovascular procedures for focal crural arterial disease in patient with CLTI, open revascularisation for infrapopliteal disease for limb salvage,[60] and endovascular and open procedures in people with diabetes and tissue loss, gangrene, or rest pain[61].

One randomised controlled trial (BEST-CLI) was conducted in participants with infrainguinal PAD and tissue loss/gangrene deemed suitable for either endovascular first or open revascularisation first approaches.[56] Inflow disease (from aorta to the common femoral artery) was corrected before or at the time of infrainguinal intervention. The trial was designed as two parallel-cohorts: (Cohort 1) participants who had adequate single segment great saphenous vein available for use as a bypass conduit, and (Cohort 2) participants without adequate single segment great saphenous vein who required use of an alternate conduit. A sub-analysis in people with diabetes for the primary outcome major adverse limb event or death was undertaken.

Outcomes reported were variable. DFU healing was reported in 3 studies,[54,55,62] one study reported healing post minor amputation (transmetatarsal amputation) and one study reported minor amputation as an outcome.[62] Seven studies reported on major amputation,[54,57–62] 4 studies reported on limb salvage[44,53,55,60] and 3 studies reported on amputation-free survival,.[44,55,58] Survival was reported in 4 studies[44,53,55,57] and mortality in 4 studies.[58–60,62] The randomised controlled trial[56] reported the composite outcome of major adverse limb event or death. Follow-up times were variable ranging from 6 months to 6 years.[54,60] Reporting of other adverse events was variable and included emergency re-admission, acute kidney injury, myocardial infarction, incisional and procedural complications, restenosis, reinterventions and perioperative mortality (Supplementary Table S2).

3.3.2 | Methodological quality and certainty of evidence

Ten of the 11 included studies were cohort studies with inadequate description of participant allocation to meet ROBINS -I criteria for non-randomised trials. These 10 studies were therefore assessed with the NOS (Table 1). The final study was a randomised controlled trial (BEST-CLI) with parallel cohorts and was assessed using the Cochrane RoB 2 tool. All cohort studies were retrospective. Most studies were categorised as having a high risk of bias with the NOS. The risk of bias was most frequently related to the heterogenous nature of patient populations, the potential effect of confounding factors on study outcomes and in some instances lack of clarity relating to loss to follow up. For these reasons, the certainty of evidence was rated as very low. The BEST-CLI randomised controlled trial was deemed to have a low risk of bias across all domains of the Cochrane RoB 2 tool (Table 2). The majority of participants had diabetes (71.8%) and a subanalysis was reported for this group. The results in this subset did not differ from the total population and were statistically significant; however, the study was not a priori powered to perform such an analysis. Therefore, confidence in the effect estimate was moderate, with the true effect considered to be likely to be close to the estimate of the effect in the total population but with a possibility that it may be substantially different. The certainty of evidence was therefore deemed to be moderate.

3.3.3 | Outcomes

Healing

Two studies evaluated healing for DFU[62] and post-transmetatarsal amputation.[57] Both reported a significant difference in healing outcomes between those undergoing endovascular and open revascularisation procedures. One study[62] retrospectively evaluated healing outcomes in 312 people undergoing endovascular tibial intervention and 105 having an open revascularisation to an inframalleolar target with healing outcomes at 6 months being significantly higher in the endovascular group (Endo: 29% and Open: 22.4%, $p = 0.02$). One study[57] reported healing outcomes post-transmetatarsal amputation as both healed at the end of follow-up (median 2.5 years) and healed at any time point. At follow-up, a significantly higher proportion of people undergoing open revascularisation had healed (Endo: 49%, Open: 66.3%, $p = 0.02$). This was consistent with results for transmetatarsal amputation healing at any time point where there was a significant difference between surgical procedures with healing occurring in 54.9% of the endovascular group and 75.9% of the open revascularisation group $p = 0.003$. In two other studies that compared outcomes of first-time open revascularisation versus first-time percutaneous transluminal angioplasty in participants with CLTI[54] and open revascularisation versus peripheral vascular intervention for tissue loss,[55] no significant differences were observed in healing outcomes at 6 and 12 months respectively.

Minor amputation

One study reported no significant difference in further minor amputations (midfoot) between endovascular and open revascularisation in CLTI participants after transmetatarsal amputation (Endo: 7.8%, Open: 4.8%, $p = 0.41$).[57]

Major amputation

In the 7 retrospective studies reporting on major amputation, 4 studies reported no statistically significant difference between endovascular and open revascularisation bypass groups[54,57,61,62] and 2 studies reported descriptive statistics only.[59,60] In participants undergoing endovascular and open infragenicular revascularisation for rest pain or tissue loss, 1 study[59] reported major amputation rates after endovascular intervention and open revascularisation of 12% ($n = 181$) and 15% ($n = 55$), respectively. The remaining study reported a significant difference between endovascular and open groups in the proportion of people undergoing major amputation. Those having an open revascularisation procedure were more likely to have a major amputation at both 1 and 5 years follow-up (1 year: Endo: 1003 [4%] and Open: 370 [5.8%], odds ratio [OR] 1.358 $p < 0.001$; 5 years: Endo: 654 [6.6%] and Open: 292 [10.1%] OR 1.481 $p < 0.001$).[58] In addition, although one study[57] reported no significant difference between interventions in major amputation rates, there was a significant difference between groups for the level of amputation. More below knee amputations occurred in the endovascular group (Endo: 25 [24.5%], Open: 10 [12.1%], $p = 0.03$) while more above knee amputations occurred in the open group (Endo: 2 [2%] Open: 7 [8.4%], $p = 0.04$).

Limb salvage and amputation-free survival

Rates of limb salvage were reported in four retrospective studies.[44,53,55,60] One study reported limb salvage rates descriptively at 1-, 3- and 6-year time intervals with little difference between

TABLE 2 Summary table of results from RoB 2 bias analysis of randomised controlled trials.

Article	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Farber (2022)	+	+	+	+	+	+

Note: D1: Bias arising from the randomisation process, D2: Bias due to deviations from intended intervention, D3: Bias sdue to missing outcome data, D4: Bias due to measurement of the outcome, D5: Bias in selection of the reported result. Judgement +: Low, ?: Some concerns, x: High.

groups.[60] Two studies found no statistical difference between endovascular and open groups[53,55] and 1 study reported increased rates of limb salvage in the endovascular group at a mean follow-up time of 18 months (Endo: 88%, Open: 73%, $p = 0.01$).[44]

Amputation-free survival was reported in 3 retrospective studies.[53,55,58] No significant difference in rates of amputation-free survival was reported across the 3 studies at follow-up points of one[55,58] and 3 years.[53]

Mortality and survival

Four retrospective studies reported mortality rates. Two studies reported descriptive statistics only. One study[60] reported mortality rates at 30 days and anytime during the follow-up period (6 years). A higher mortality rate occurred in the endovascular group at 30 days (Endo: 5/84 [6%], Open: 3/130 [2.3%]), but there was a higher mortality rate in the open group during the follow-up period (Endo: 26/84 [31%], Open: 64/130 [49%]). A second study[59] also reported slightly higher mortality in the open group at 1 year (Endo: 80 [6%], Open: 36 [10%]). Two studies reported statistically significant differences between endo and open groups.[58,62] At 1-year follow-up, 1 study[62] reported that the mortality rate in the endovascular group was more than double that of the open group (30% vs. 14%). Similarly, a second study[58] reported a statistically significant (after adjusting for confounders) decrease in the likelihood of death at 5 years follow-up in the open group (OR 0.841 $p = 0.02$).

Four studies reported on survival in endovascular and open revascularisation and found no significant difference between groups at follow-up ranging from 1 to 3 years.[44,53,55,57]

The BEST-CLI randomised controlled trial reported on a composite outcome of major adverse limb event or death for participants with infrainguinal PAD who were deemed suitable for endovascular first or open revascularisation first approaches and were randomised into two parallel cohorts as previously described.[56] In Cohort 1, the great saphenous vein (open) bypass first approach (510 participants with diabetes) was superior to endovascular therapy first (509 participants with diabetes) to prevent a major adverse limb event or death in participants with diabetes (hazard ratio 0.72; 95% CI [confidence interval] 0.61–0.86) with benefit comparable to those without diabetes (hazard ratio 0.57; 95% CI 0.41–0.78). In Cohort 2 (participants requiring an alternate conduit for bypass), this primary outcome was similar between the endovascular and open groups and there was no apparent benefit of one intervention over the other (hazard ratio 1.03, 95% CI 0.70–1.53).

3.3.4 | Evidence statements

In people with diabetes, peripheral artery disease and either a foot ulcer or tissue loss in whom infrainguinal revascularisation is indicated and who are suitable for either open or endovascular approaches, and who have an adequate single segment of saphenous vein, open revascularisation surgery is superior to endovascular revascularisation to prevent a major adverse limb event or death.[56]

Certainty of evidence: moderate.

In people with diabetes, PAD and tissue loss and/or gangrene, for whom there is no clinical equipoise regarding revascularisation strategy, or the single saphenous vein is unsuitable for open surgery, there is inadequate evidence to determine whether endovascular revascularisation is superior to open or hybrid revascularisation to heal a foot ulcer or prevent minor or major amputation.[44,53–55,59–62]

Certainty of evidence: very low.

4 | DISCUSSION

This systematic review identified 26 studies investigating the outcomes of healing, minor and major amputations, amputation-free survival, limb salvage, mortality and survival for DR and IR in people with diabetes and tissue loss. Eleven studies investigating the same outcomes for endovascular and open revascularisation approaches were identified. No study reported outcomes for hybrid revascularisation procedures separately. Overall, the studies were of very low quality with high risk of bias.

In the majority of studies, wound healing and major amputation outcomes were better for DR than IR for both open and endovascular procedures. In contrast, amputation-free survival, limb salvage and mortality outcomes were inconsistent. However, these findings are limited by the lack of data synthesis and multiple confounders, variable follow-up periods, heterogenous populations and use of cohort study designs.

There are few data to support differential outcomes for IR versus DR following open revascularisation. In fact, the peroneal artery is frequently the least likely calf artery to be occluded in diabetes[63] and a commonly employed bypass target though it has the smallest territory of DR in theory. Fourteen of the studies investigated the outcomes of DR and IR for endovascular procedures. Most of these studies reported a higher proportion of participants receiving DR healed compared to those receiving IR, including one study using propensity score matched pairs (DR:69%, IR: 47%).[46] However, of 5 studies evaluating IR and IRc outcomes separately,[8–11,31] IRc was shown to be associated with better healing outcomes than both DR and IR in 3 studies[8,10,31] and better than IR in 2 studies.[9,11] These findings suggest that IRc is similarly effective as DR for healing. The lack of differentiation between IRc and IR for healing, amputation and mortality outcomes may have affected the magnitude of difference between DR and IR results for all revascularisation interventions. Furthermore, difficulty allocating foot and ankle ulcers to corresponding angiosomes and the presence of multiple wounds and dual angiosomes may also have influenced the outcomes of the studies included in this review. Kret et al.[15] found that only 36% of wounds in their series corresponded to a single distinct angiosome. Another study[16] determined that approximately 20% of all DFU and over 50% of toe wounds could not be accurately classified according to angiosomes. The authors concluded that there are challenges in classification related to the presence of multiple wounds and dual angiosomal supply of wounds that will likely reduce the capacity of

the angiosome model to optimise revascularisation strategies.[16] In this current review, where tissue loss involved more than one angiosome, one study[32] considered revascularisation of the angiosome supplying the largest surface of the wound as constituting DR. In addition, when multiple wounds were present in different angiosomes, DR was only accomplished according to the authors when each angiosome was revascularised, highlighting the complexity of assessing angiosome-based revascularisation.[32]

Of the 11 studies retrieved comparing endovascular to open revascularisation for outcomes of healing, minor and major amputation, amputation-free survival, limb salvage, and mortality, 10 of these studies were observational cohorts that lacked details of participant allocation. The data from these studies suggest that for healing, amputation and mortality, there is no consistent evidence that either endovascular or open revascularisation is superior. However, the inconsistency in study outcomes is likely to reflect the heterogenous nature of the participant populations, the range of endovascular techniques and open revascularisation methods across and within studies, and the low overall quality of the majority of available evidence. Selection bias is a major concern among these non-randomised trials as participants undergoing open or endovascular procedures are likely very dissimilar in terms of comorbidity burden, anatomic severity of disease, and other key factors.

The BEST-CLI study was the only randomised controlled trial identified that included an analysis of participants with diabetes, met the inclusion criteria for this review and achieved homogeneity in participant population and surgical technique.[56] Significantly, this trial specifically related to the treatment of infrainguinal disease in (1) participants who had adequate single segment great saphenous vein available for use as a bypass conduit, and (2) participants without adequate single segment great saphenous vein who required use of an alternate conduit. The enrolment of each participant in the study hinged on clinical equipoise at each enrolling site meaning that those performing endovascular and open revascularisations felt that either option was possible, reasonable, and likely to yield a favourable outcome. This resulted in a participant population that was homogenous. The study demonstrated that among these participants with CLTI due to infrainguinal PAD, who were deemed suitable for either approach and had an adequate great saphenous vein available for bypass, a composite primary outcome of major adverse limb event (above ankle amputation, major index limb reintervention [new bypass, interposition graft revision, thrombectomy or thrombolysis]) or death was significantly reduced in the surgery first arm including those participants with diabetes (hazard ratio 0.72; 95% CI 0.61–0.86).[56] However, for participants without an adequate single segment great saphenous vein available, there was no clear benefit of one approach over the other. Although undertaken as a sub-analysis (and the analysis was underpowered for the primary outcome), the analysis of the diabetes cohort supports the use of open revascularisation surgery in people with diabetes with an adequate single segment great saphenous vein.

Revascularisation in people with diabetes and PAD is challenging due to more distal distribution of disease in the lower limb, including frequent presentation of infragenicular arterial occlusive disease.[18–20] In this population, PAD is often bilateral and multisegmental with impaired collateral formation, long segment tibial artery occlusions and a high prevalence of medial arterial calcification.[18–20] Specific investigation in this population is therefore required to inform surgical practice. While there have been a number of investigations into endovascular and open surgical revascularisation outcomes in populations with CLTI (including the Bypass vs. Angioplasty in Severe Ischaemia of the Leg [BASIL] randomised controlled trial), lack of outcome analysis for participants with diabetes limits the application of these findings for surgical management of PAD in this population.[21] Of note, the Surgical Reconstruction Versus Peripheral Intervention in Patients With Critical Limb Ischaemia (SPINACH) Study used propensity score matching of 548 participants with CLTI, the majority of whom had diabetes (~75%) to investigate amputation-free survival rates in participants either with or without suprainguinal disease, undergoing planned open or endovascular revascularisation procedures.[22] The study demonstrated that the 3-year amputation-free survival rate was not different between open revascularisation and endovascular revascularisation in the overall CLTI population. Risk stratification analysis showed that open revascularisation had better outcomes in participants with severe limb status. For participants with comorbidities that increased surgical risk, for example, poorly managed or severe cardiovascular disease, diabetes and renal disease, better outcomes were associated with endovascular intervention.[22] However, the presence of diabetes was one of 10 factors that contributed to a favourability score for open revascularisation and data for this population were not analysed separately.

The findings of this review highlight the limited evidence comparing outcomes for DR and IR and endovascular and open revascularisation for diabetes-related foot disease, including healing and amputation. As previously discussed, the interpretation of existing data is limited by high heterogeneity in participant populations, heterogeneity in endovascular and open revascularisation procedures and challenges with the classification of DR and IR procedures. Lack of clinical homogeneity of participants enrolled at baseline and lack of propensity matching for confounding factors in the majority of studies are likely to have affected outcomes.

The timeframe for the search for this systematic review extended to 1980 with included studies published between 2000 and 2022. Due to advances in endovascular techniques and equipment over this time period, it is likely that results of older studies may not accurately reflect outcomes that may be achieved at present. Further high quality randomised controlled trials in homogenous populations are required to advance evidence-based treatment protocols for revascularisation in people with diabetes and PAD in relation to both DR and IR and endovascular and open surgical approaches. Future research requires more complete reporting of the degree of limb threat (eg. WIfI classification), presence or absence of infection, the availability of vein conduit, and sufficient anatomic details about the extent and severity of lesions treated and procedures undertaken.[24,64] Incorporation of, and stratification by the degree of limb

threat and use of a standardised system such as the recently developed Global Limb Anatomic Staging System to estimate the likelihood of success and patency of arterial pathway revascularisation based on the extent and distribution of disease may be useful to assist in standardising reporting in future research.[24] In addition, this review does not summarise the data relating to technical success or feasibility of revascularisation in people with diabetes or outcomes relating to ambulation, patient preference, or quality of life. The choice of methods for revascularisation should not be solely based on vascular anatomy but should be part of a process of shared decision-making that includes the consideration of overall patient risk, limb threat severity, the availability of autogenous vein conduit, and patient preferences.

4.1 | Limitations

While the search methods employed in this study were designed to be robust and included the use of a validation set of studies known to the researchers to test the search strategy, there may be some evidence that was not captured. Researchers in the field were not contacted for unpublished studies, authors were only contacted where information from included articles was missing, or it was identified that relevant data may have been collected as part of the study. The lack of suitability of data for meta-analysis also limits the extent to which the study findings can be collectively interpreted.

5 | CONCLUSION

The majority of available evidence for the effectiveness of DR versus IR and open versus endovascular revascularisation for improving wound healing, prevention of minor and major amputations, and adverse events in people with diabetes, PAD and tissue loss is inconclusive. Moreover, the certainty of evidence is mostly very low. Data from a sub-analysis within one randomised controlled trial supports the use of open revascularisation over endovascular revascularisation to prevent a major adverse limb event and mortality in people with diabetes, tissue loss and infrainguinal disease who have an adequate great saphenous vein available and are suitable for either approach. Further high quality randomised controlled trials in homogenous populations are required to advance evidence-based treatment protocols for revascularisation in people with diabetes and PAD.

AUTHOR CONTRIBUTIONS

Vivienne Chuter designed the search strings, performed the literature search, assessed the literature, extracted data and drew conclusions, checked and completed the risk of bias tables, and wrote the manuscript. Robert Fitridge assessed the literature, extracted data, completed the risk of bias tables, drew conclusions and co-authored the manuscript. Nicolaas Schaper assessed the literature, extracted data and drew conclusions. All authors were responsible for developing the clinical questions, selecting the outcomes, formulating the PICOs, and all authors critically reviewed the conclusions and the manuscript. Vivienne Chuter acted as the secretary of the working group and Robert Fitridge as the chair of the working group. Vivienne Chuter and Robert Fitridge take full responsibility for the content of this publication.

ACKNOWLEDGEMENTS

We would like to thank the following external experts for their review of our PICOs for clinical relevance and the Guideline document: Sriram Narayanan (Singapore), Rica Tanaka (Japan), Ismail Cassimjee (South Africa), Xu Jun (China), Heidi Corcoran (Hong Kong), Yamile Jubiz (Colombia), Tsvetalina Tankova (Bulgaria). We would like to thank Frank Quigley and Jens Carsten Ritter (Australia) as independent external experts, and Jaap van Netten (on behalf of the IWGDF editorial board) for their peer review of the manuscript. Production of the 2023 IWGDF Guidelines was supported by unrestricted grants from Advanced Oxygen Therapy Inc., Essity, Mölnlycke, Reapplix, and Urgo Medical. These sponsors did not have any communication related to the systematic reviews of the literature or related to the guidelines with working group members during the writing of the guidelines and have not seen any guideline or guideline-related document before publication.

Open access publishing facilitated by Western Sydney University, as part of the Wiley - Western Sydney University agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST STATEMENT

Production of the 2023 IWGDF Guidelines was supported by unrestricted grants from Advanced Oxygen Therapy Inc., Essity, Mölnlycke, Reapplix, and Urgo Medical. These sponsors did not have any communication related to the systematic reviews of the literature or related to the guidelines with working group members during the writing of the guidelines and have not seen any guideline or guideline-related document before publication. Full conflict of interest statements of all authors can be found online at www.iwgdf-guidelines.org.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ETHICS STATEMENT

Ethics approval was not required for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Chuter V, Schaper N, Mills J, et al. Effectiveness of revascularisation for the ulcerated foot in patients with diabetes and peripheral artery disease: a systematic review. *Diabetes Metab Res Rev*. 2023;e3700. https://doi.org/10.1002/dmrr.3700