The utilisation of vascular limb salvage services in the assessment and management of chronic limb-threatening ischaemia and diabetic foot ulceration: A systematic review

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Abstract
Specialist vascular limb salvage services have gained prominence as a new model of care to help overcome barriers which exist in the management of patients with chronic limb-threatening ischaemia (CLTI) and/or diabetic foot ulceration (DFU). This systematic review aims to explore the nature of reported services, investigate their outcome in the management of CLTI/DFU, and assess the scope and quality of the evidence base to help make recommendations for future practice and research. A systematic search of MEDLINE, Embase, The Cochrane Library, Scopus and CINAHL, from 1st January 1995 to 18th January 2019, was performed. Specialist vascular limb salvage services were defined as those services conforming to the definition of “centres of excellence” within the 2019 Global Vascular Guidelines. A study protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42019123325). In total, 2260 articles were screened, with 12 articles (describing 11 services) included in a narrative synthesis. All services ran akin to the “toe-and-flow” model, with a number of services having additional core input from diabetology, microbiology, allied health professionals and/or internal/vascular medicine. Methodological weaknesses were identified within the design of the included articles and only one was deemed of high quality. The inception of services was associated with improved rates of major amputation; however, no significant changes in minor amputation or mortality rates were identified. Further research should adopt more a standardised study design and outcomes measures in order to improve the quality of evidence within the literature.

KEYWORDS
amputation, critical pathways, diabetic foot, limb salvage, peripheral arterial disease

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1  |  INTRODUCTION

The approach to managing chronic limb-threatening ischaemia (CLTI) and diabetic foot ulceration (DFU) has been transformed over the last 30 years, in part due to two fundamental changes. First, the advent of the endovascular era has radically changed how patients are managed and provides treatment options to those who were once deemed unsuitable for revascularisation. Second, is the recognition of the role that ischaemia plays in the aetiopathology of DFU. Peripheral arterial disease (PAD) is highly prevalent in patients with diabetic foot disease; the assessment of the peripheral vasculature and subsequent revascularisation are therefore key components of ulcer management.¹ ² This recognition has led to a global shift in how CLTI should be defined, with greater emphasis on a broader and more heterogeneous definition. This new definition highlights the interaction between ischaemia, wound complexity and infection in the natural history of ulceration and aetiology of limb loss.³ The definition also helps to homogenise care for patients with limb ischaemia and/or DFU.

Many problems, however, still exist within the referral and management pathways for patients, often resulting in lengthy time delays in accessing vascular services.⁴ Two recent surveys of healthcare professionals both identified difficulties with accessing specialist vascular consultation and non-invasive imaging as major barriers to care.⁵ ⁶ This defies the contemporary trend towards greater multidisciplinary and collaborative working. While vascular surgeons are now established members of the multidisciplinary team (MDT) for managing patients with DFUs, many centres and MDT services (eg, MDT diabetic foot clinics) do not provide direct access to vascular assessment, imaging and revascularisation.⁷

In response to this, the idea of a specialist limb salvage service has been gaining prominence as a new model of care, which builds upon the MDT concept to help overcome these barriers. Fitzgerald and colleagues⁸ provided the first definition of these services, describing seven essential skills required to deliver a limb salvage service in the context of managing DFUs. These included the ability to assess and manage PAD and neuropathy, and perform debridement and drainage of infection. In order to deliver this, input from specialists in vascular surgery and podiatry (or equivalent specialties) were described as the minimum to form an effective service.⁹ This has led to what has been described as the “toe-and-flow” model of conjoined care; comprising a team who can assess and manage ischaemia, and provide complex lower limb wound care and ulcer prevention strategies.

Building upon this, Rogers and colleagues⁹ established the idea of tiers of care for the management of DFUs. These range from community-based “basic” providers to “centres of excellence,” which provide specialist limb salvage services. “Centres of excellence” usually run within a university/teaching hospital. They offer regional and/or national referrals for complex cases, provide a full spectrum of multidisciplinary specialist input and run educational services.⁹

While these limb salvage services have been described principally in the care of patients with DFUs, they are now also being considered within the context of the broader definition of CLTI. Subsequently, the recently published Global Vascular Guidelines (GVG) have further developed the idea and defined criteria for vascular limb salvage “centres of excellence.”¹⁰ Unlike traditional MDT services, which may not have provision to manage ischaemia, these vascular limb salvage services provide dedicated access to vascular specialists who manage PAD, in addition to specialities who provide complex wound and medical care. Furthermore, they also provide care to patients without diabetes.

To date, no review has used the GVG criteria to explore limb salvage services within the literature or evaluated the evidence base to support their use. This systematic review therefore aims to: (a) explore the nature of these services within the literature, (b) investigate their outcomes in the management of CLTI/DFU and (c) assess the scope and quality of the evidence base to make recommendations for future research.

2  |  METHODOLOGY

This systematic review was performed in accordance with the "Meta-analysis of Observational Studies in Epidemiology" (MOOSE) specification.¹¹ A study protocol was designed conforming to the Preferred Reporting Items for Systematic Review of Meta-analysis Protocols (PRISMA-P)¹² and registered at the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42019123325).

2.1  |  Search strategy

A search of MEDLINE, Embase, The Cochrane Library, Scopus and CINAHL was performed on 18th January 2019. A search strategy was employed using combinations of keywords and thesaurus headings, including: “limb ischaemia,” “diabetic foot,” “foot ulcers,” “wound clinic,” “perfusion clinic,” “toe and flow,” “limb preservation,” “amputation” and “wound healing.” Only English language articles were considered. The search strategy was developed in MEDLINE and adapted accordingly for use with other databases (Appendix S1). From preliminary searches a number of historical articles potentially meeting the inclusion criteria were identified. Therefore, in order to provide a thorough overview of all services meeting the inclusion criteria, articles published from first January 1995 onwards were considered. For each included article, bibliographic lists were screened for additional articles of interest. Additional internet searches were also performed, utilising Google and Google Scholar (Google LLC). The searches were developed and performed by investigator AN. The searches were repeated prior to completion of the study (July 17, 2019).

2.2  |  Types of studies

All observational studies (except case reports), qualitative research, conference abstract and audits were included. Given the
heterogeneous nature of the management of CLTI/DFU across healthcare systems, only articles based within “high-income” countries (annual GDP > $15 000 per capita) were eligible.

2.3 | Study participants

Articles involving adult patients (>18 years) with a presumed or confirmed diagnosis of CLTI/DFU were included. Articles which presented data on ulcers of other aetiology were excluded unless data were presented separately from CLTI/DFU results.

2.4 | Intervention

This review focussed on services defined as specialist vascular limb salvage “centres of excellence” as defined within the 2019 GVG. These centres were defined by the following four characteristics:

• Consists of a specialist team who can provide both medical and surgical management of PAD (ie, vascular surgery or interventional radiology) and infection (eg, podiatry, orthopaedics, plastic surgery or other specialty that perform surgical debridement), and provide general and intensive medical care

• Protocol-drive care:

• The service follows evidence-based clinical protocols, procedures and pathways.

• Outcome monitoring and improvements:

• Have an established process for data collection and reporting data to the literature

• Have an established process for continual improvement based upon outcomes and new techniques

Education:

• Serves as an educational resource for the medical community via mentoring, publishing, teaching or conferences.

For the purposes of this study, services must provide daily patient review plus vascular review more than twice per week. Acknowledging that specific speciality roles (particularly podiatry) vary between healthcare systems, the description of individual responsibilities within the reporting article were used to judge for study inclusion. Given the potentially novel and developing nature of some services, educational pathways may yet to be established and therefore articles were not excluded solely upon this criterion.

2.5 | Outcomes

For individual articles, baseline data were extracted. This included study design, sample size, publication date, inclusion/exclusion criteria and number of patients with CLTI/DFU. Details on individual services were also collected, including core specialities (specialities who function within the service without onward referral), treatment scope and education services.

Individual outcomes of this review are shown in Table 1. For the purposes of this review, major amputation rate (1 year and total) was the primary outcome.

2.6 | Data extraction

A process of data extraction was formulated in line with the Cochrane Handbook for Systematic Reviews of Interventions.12 Duplicates were

| Outcome | Timing | Definition |
|---------|--------|------------|
| Major amputation rate (amputation proximal to ankle joint)* | 1 year | Total N° major amputations/Total N° patients at 1 year and the end of the individual study |
| Minor amputation rate (amputations distal at or distal to ankle joint) | End (total) | Total N° minor amputations/Total N° patients by end of the individual study |
| High-low amputation rate | End (total) | Total N° major amputations/Total N° minor amputations by the end of the individual study |
| Amputation free survival rate | 1 year | Total N° patients alive and without undergoing a major amputation/Total N° patients (at 1 year) |
| Rate of wound healing | End (total) | As defined by individual studies |
| Mortality rate | 1 year | Total N° deaths/Total N° patients at 1 year and the end of the individual study |
| Number of revascularisation procedures | End (total) | Total N° patients undergoing at least one revascularisation procedure by the end of the study/Total N° patients by end of the individual study |

*aPrimary outcome.
first removed using EndNote X9 (Clarivate Analytics) with titles and abstracts being independently reviewed by A.N. and B.B. for inclusion. The full texts of suitable articles were then assessed for final inclusion by A.N. with independent assessment provided by J.H. and B.B. Subsequent data extraction was performed by A.N. with independent data collection provided by S.N. and A.E.A. On completion of each step, results were cross-checked and discussed between team members. Any disagreements were resolved through discussion.

In cases where two articles describe the same service and outcomes, only the most contemporary article was included. Likewise, where the same cohort is described in different articles (albeit presenting different outcomes), baseline data were only recorded once. In cases where further detail was required to interpret results, the corresponding author was contacted (where possible) through their published email address.

2.7 | Quality assessment

Methodological quality was assessed using the appropriate study type critical appraisal tool published by the Joanne Briggs Institute.\(^{13}\) For cohort studies (anticipated as the most likely study type), articles meeting fewer than 6 criteria were deemed low, 6 to 9 moderate and greater than 9 high quality. Quality assessment was performed by A.N. with independent assessment provided by A.E.A. and S.N., following data extraction. Disagreements were resolved through discussion. No tools currently exist to assess conference abstract or published audits.

2.8 | Data synthesis

From initial searches the observed heterogeneity between articles led to the anticipation that a formal meta-analysis would not be possible and as such was not the basis of this review. A narrative synthesis of results was conducted with amputation-related outcomes being tabulated. Where data were available, the “high-low” amputation rate was calculated. If not presented,\(^{14}\) Furthermore, Pearson’s \(\chi^2\) test was utilised to test for statistical significance in situations where categorical data were provided without being tested for statistical significance. Analysis was undertaken using SPSS v25.0 (IBM Corp., Armonk, USA) with \(P < .05\) deemed statistically significant.

3 | RESULTS

On completion of the search strategy 2260 articles were screened, with 12 articles\(^{15}-26\) being included in the final synthesis (Figure 1). The characteristics of the included articles are shown in Table 2. Eleven articles\(^{15,18,20-26}\) were retrospective cohort studies. Gottrup\(^{19}\) published a descriptive piece without outcome data, although case-load data were presented. Overall, data on 4010 patients treated within limb salvage services were presented. Hsu\(^{25}\) provided no sample size data and Williams\(^{26}\) reported data across different dates, thus limiting the article’s application as major and minor amputation rates could not be accurately calculated.

3.1 | Study quality

Results of the quality assessment process are shown in Appendix S2. Only one article\(^{26}\) was deemed of “high” quality. Five articles\(^{15,17,22,23,25}\) were “moderate” quality with five articles\(^{16,18,20,21,24}\) deemed of “low” quality. The article by Gottrup\(^{19}\) could not be quality assessed.

Particular methodological issues are worthy of mention. Only six articles\(^{15-17,20,24,26}\) reported comparative institutional data in order to provide context to their results. Additionally, only six articles\(^{15,17,22,23,25,26}\) reported sufficient baseline data to help identify potentially confounding factors, notably the severity of ischaemia or presence of neuropathy. Of these, only Flores\(^{26}\) provided statistical adjustment for potential confounders when comparing data.

3.2 | Structure of limb salvage services

The detailed structure and description of each service is shown in Appendix S3. Eleven articles\(^{15,16,18-26}\) described individual limb salvage services, with two articles by Driver\(^{17,18}\) describing the same facility twice, although presenting different outcomes. Four services\(^{15,16,18,25}\) exclusively managed patients with DFU, with a further three services\(^{11,23,24}\) offering care to patients with CLTI. Van Gils\(^{22}\), Gottrup\(^{19}\) and Flores\(^{26}\) all described more extensive services, providing assessment and treatment of a wide aetiology of wounds.

Where described, all services were based within an existing hospital setting. Five services\(^{14,16,19,20,23,24}\) provided both acute inpatient and outpatient care. Flores\(^{26}\) described an “affiliate” outpatient wound care centre, which provided access to inpatient vascular services. Three others provided solely outpatient care.\(^{18,22,25}\) Both Sanguily\(^{21}\) and Alexandrescu\(^{15}\) did not clearly describe the setting of their service.

In line with the GVG guidelines,\(^2\) all services ran as part of a MDT akin to the “toe-and-flow” model at their core. The provision of other core specialities varied, with four services\(^{15,19,20,25}\) providing specialist input from diabetology and two services\(^{19,26}\) providing input from internal/vascular medicine (Figure 2). Armstrong,\(^16\) Vartianian\(^23\) and Van Gils\(^22\) also reported collaboration with other specialities, including cardiology, nephrology and prosthetics, on an “as required” basis. Of noteworthy mention, Gottrup\(^{19}\) described a highly comprehensive service which included care from specialists in diabetology, internal medicine, infectious disease, allied health and general surgery, in keeping with the wide variety of wound problems they managed.

3.3 | Education

Only four services\(^{18,19,21,22}\) provided an educational resource for clinicians. Driver\(^{18}\) and Gottrup\(^{19}\) both described providing provision for clinical placement experience at their centre to learn wound care
techniques, with Gottrup providing a formal nursing diploma. Driver\textsuperscript{18} also reported organising an interdisciplinary conference to provide workshops and discussion with regards to diabetic limb preservation. Furthermore, Van Gills\textsuperscript{22} and Sanguily\textsuperscript{21} both provided staff education regarding their services with Sanguily\textsuperscript{21} also educating on the awareness of “high-risk” patients.

3.4 | Rates of major amputation

Ten articles\textsuperscript{15-18,20-23,25,26} reported major amputation related outcomes, as shown in Table 3. Of these, Alexandrescu\textsuperscript{15} and Flores\textsuperscript{26} reported major amputation based upon number of limbs managed, rather than total patients. No articles reported amputation-free survival data. Four articles\textsuperscript{15,16,20,26} compared the rates of major amputation with local institutional data (either from prior to inception or patients not seen in their service), with all but one of these articles describing services focussing on the care of patients with DFUs.\textsuperscript{26}

Only Flores\textsuperscript{26} provided a comparative 1-year major amputation rate, identifying a significant reduction as a proportion of total limbs (pre-service = 8.8%, service = 5.5%, \(P = .04\)). While this was based upon a 46% increase in the number of limbs assessed, the service managed a significantly higher proportion of patients with rest pain and DFU since inception of their service.
| Author       | Year of publication | Study type | Inclusion criteria                                                                 | Exclusion criteria                                                                                                                                                                                                 | Comparative data | Sample size (patients) (n) | DFU (n) | CLTI (n) | Follow-up duration (months unless stated) |
|--------------|---------------------|------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|---------------------------|---------|---------|-----------------------------------------|
| Van Gills    | 1999                | RC         | All patients evaluated within the service (1st October 1991 to 31 September 1992) | <4 clinic visits prior to amputation, death or study end, or had an amputation within 1 month of clinic enrolment                                                                                               | b                | 124           | 90      | 50       | 55                                      |
| Gottrup      | 2001                | Descriptive piece | N/A                                                                                       | b                                                                                                                                                                                                                | N/A             | N/A                      | N/A     | N/A     | N/A                                      |
| Driver       | 2005                | RC         | All patients with diabetes (ICD-9250–250.9) undergoing any amputation (1999 and 2003) | b                                                                                                                                                                                                                | b               | (9841 cases)            | b       | b       | b                                        |
| Zayed        | 2009                | RC         | All patients with diabetes and CLTI (Dec 2003-May 2006)                                  | b                                                                                                                                                                                                                | b               | 312           | 312     | 312      | Until symptoms free                   |
| Alexandrescu | 2009                | RC         | All consecutive patients with ischaemic/neuro-ischaemic wounds undergoing multilevel revascularisation (September 2001–March 2008) | Patients with Wagner grade 5 lesions (where primary amputation unavoidable), acute ischaemia, aneurysmal disease or iodine media intolerance                                                                      | b               | 163           | 163     | 163      | Mean = 23.3 months (range 1–68 months) |
| Driver       | 2010                | RC         | Random selection of patients with diabetes from overall population of patients with diabetes | Patients with less than 3 year follow-up                                                                                                                                                                      | b               | 485           | 485     | 14       | Minimum 36 months                     |
| Armstrong    | 2012                | RC         | All patients with diabetic foot complications requiring foot surgery or vascular intervention (2006–2010) | Patients requiring elective surgery who had intact protective sensation                                                                                                                                          | b               | 374           | 374     | ND       | 288 interventions for PAD            |
| Vartanian    | 2015                | RC         | Patients at "highest risk" for limb loss - diabetic foot ulcers or ischaemic wounds (ulcer or gangrene, with ankle pressure of <50 mmHg or toe pressure of <30 mmHg, however in some cases vascular imaging was not available so decision was made on clinical assessment). | Patients with "benign conditions" (arthritis, overuse injury, simple infection in non-diabetic patients, venous ulcers, trauma or radiculopathy referred for second opinion and sent back to referrer for treatment or not followed-up after initial examination) | b               | 89            | 62      | 61c      | Median = 6.8 (range 1.7–17.0) months |
| Author   | Year of publication | Study type | Inclusion criteria                                                                 | Exclusion criteria | Comparative data                                                                 | Sample size (patients) (n) | DFU (n) | CLTI (n) | Follow-up duration (months unless stated) |
|----------|---------------------|------------|-------------------------------------------------------------------------------------|-------------------|----------------------------------------------------------------------------------|----------------------------|---------|----------|------------------------------------------|
| Hsu      | 2015                | RC         | All patients with diabetic foot disease (ICD-9: 250.70-50.83) treated at service (2004-2013) | b                 | Patients treated prior to development of service (2004–2009)                      | b                          | b       | b        | b                                        |
| Sanguily | 2016                | RC         | All patients evaluated for PAD/CLI through angiography (2010–14)                     | b                 |                                                                                   | 1207                       | b       | 1207     | b                                        |
| Williams | 2017                | RC         | All patients requiring emergency admission for CLTI or DFU. 2015 data presented for CLTI and 2004–2009 and 2015 data for DFU | b                 | Patients with DFUs only (2004–2005)                                               | 347                        | 287     | 60       | b                                        |
| Flores   | 2019                | RC         | All patients treated by vascular surgeons at "affiliate" wound care service for claudication, CLTI or DFUs (October 2013–October 2016) | Patient requiring treatment for non-atherosclerotic PAD, acute ischaemia or venous disease | Patients treated (for same inclusion criteria) in the 3 years prior to development of service (2010-2013) | 909                        | 129     | 493      | Median = 3.7 [IQR 2.4–5.0] years         |

*Including comparative data.

bNot defined.

cPatients with impalpable pulses or with no doppler signals.

Abbreviations: CLTI, chronic limb threatening ischaemia; DFU, diabetic foot ulceration; ICD, International Classification for Disease 9/10 code; IQR, interquartile range; N/A; Not available; PAD, Peripheral arterial disease; RC, Retrospective cohort.
Four articles\cite{15,16,20,26} reported a reduction in the total rates of major amputation following inception of their services; however, how rates were calculated and reported was heterogeneous. Flores\cite{26} identified a reduction in the adjusted overall risk of major amputation (HR 0.41, 95% CI 0.27-0.62, \(P < .001\)). Both Flores\cite{26} (pre-service = 9.0%, service = 6.0%, \(P = .008\)) and Armstrong\cite{16} (\(P < .01\)) also presented significant reductions in the rate as a proportion of total procedures. Armstrong however only provided data in graphical form from which exact results could not be deduced. Patient demographic data were also not presented.

Hsu\cite{20} identified a significant reduction in the rate of major amputation for patients with DFU and a decrease in the incidence of major amputation in the total population of patients with diabetes, however, provided no sample size or patient demographic data. Alexandrescu\cite{15} reported a non-significant reduction in the rate of major amputation as a proportion of limbs (pre-service = 19.8%, service = 10.3%, \(P = .07\)), yet identified a significant increase in the chances of limb salvage (restoration of “functional autonomy” without major amputation) at 48 months (HR 2.35, 95% CI 1.04-5.30, \(P = .04\)). While numbers treated were similar between cohorts (pre-service = 86 limbs, service = 97 limbs), no comparable demographic data were presented.

Four articles\cite{17,21,23,25} reported the total major amputation rates just for their services, ranging from 3.4% to 14.5% with Van Gills\cite{22} reporting a 5% rate at 1-year.

3.5 Rates of minor amputation

Only two articles\cite{17,26} provided comparative rates of minor amputation. Flores\cite{26} identified no significant change in the proportion of patients undergoing minor amputation procedures (pre-service = 15.5%, service = 19.7%, \(P = .09\)). When combined with extensive debridement, higher rates were identified in their service (pre-service = 10%, service = 16%, \(P = .005\)). Driver\cite{17} also identified comparable rates of patients undergoing minor amputation (pre-service = 15%, service = 17%, \(P = .663\)), despite a higher proportion of patients managed within their service having high grade disease (University of Texas Grade 3; pre-service = 4%, service = 13%, \(P = .002\)) (Table 3).

Armstrong\cite{16} reported data on minor amputation as a proportion of total procedures, identifying a significant increase in the proportion of mid-/hindfoot amputation performed since inception of their service (\(P < .05\)), with a decrease in the proportion of toe amputations (\(P < .05\)). As with major amputations, data were only presented in graphical form from which an exact result could not be deduced.

High-low amputation ratios were also available within two articles\cite{16,23}. Armstrong\cite{16} provided comparative data, identifying a fall in this ratio since inception of their service.

3.6 Rates of revascularisation

A variety of revascularisation outcomes were reported; however, only three articles\cite{16,24,26} provided comparative data. Armstrong\cite{16} identified a 44% increase in the total number of revascularisation procedures being performed since inception of their service (no raw data presented). Interestingly, this rise was associated with an increase in the proportion of open revascularisation procedures (pre-service = 28.8%, service = 35.9%, \(P = .05\)) and a trend towards greater numbers of infra-popliteal procedures (pre-service = 40.7%, service = 48.8%, \(P > .05\)).

By contrast, Flores\cite{26} reported a significant drop in the number of patients requiring revascularisation (pre-service = 88.4%,
| Author       | Year | 1 year major amputation rate (%) | Total major amputation rate (%) | High/low ratio | Minor amputation rate (%) | Other amputation related outcomes                                                                                                                                 |
|--------------|------|----------------------------------|---------------------------------|----------------|--------------------------|--------------------------------------------------------------------------------------------------------|
| Van Gills    | 1999 | 5%                               | 18 (14.5)                      |                |                          |                                                                                                         |
| Driver       | 2005 |                                  |                                 |                |                          | Incidence of all amputation in patients with diabetes decreased over 5 years from service inception (9.9 vs 1.9/1000) |
| Zayed        | 2009 |                                  |                                 |                |                          |                                                                                                         |
| Alexandrescu | 2009 |                                  |                                 |                |                          | Limb salvage\(^b\) at 48 months (service vs non-service) = HR 2.35, 95% CI 1.040-5.311, \(P = .040\)    |
| Driver       | 2010 |                                  |                                 |                |                          |                                                                                                         |
| Armstrong    | 2012 |                                  |                                 | Reduction in rate\(^c\) | 0.27 0.27 | 0.35 |                                                                                  |
| Vartanian    | 2015 |                                  |                                 |                |                          |                                                                                                         |
| Hsu          | 2015 |                                  |                                 |                |                          | Incidence (per 100 000) of major amputation decreased in the total population of patients with diabetes (pre-service = 193, service = 62) |
| Sanguily     | 2016 |                                  |                                 |                |                          |                                                                                                         |
| Williams     | 2017 |                                  |                                 |                |                          | Age/gender adjusted incidence (per 100 000) of major amputation decreased in both patients with diabetes (pre-service = 412, service = 15) and without diabetes (pre-service = 7, service = 1) |
| Flores       | 2019 | 38 (5.5) 41 (8.8) .04 6.0% 9.0% | 136 (19.7) 72 (15.5) 0.09 |                |                          | No change in 30-day major amputation rate—pre-service = 2.2%, service = 2.8% (\(P = .60\))          |

\(a\)Outcome not reported.

\(b\)Freedom from amputation and restoration of functional autonomy.

\(c\)Data presented in graphical form (unable to deduce result without raw data).
service = 81.4%, P = .001). This fall however, may be a result of the increasing patient volume and higher proportion of patients with DFU, who were treated since inception of their service. Furthermore, no differences in the proportions of patients undergoing endovascular (pre-service = 63.0%, service = 66.3%, P = .3) or open first strategies (pre-service = 23.1%, service = 22.7%, P = .6) were reported. As with Armstrong, inception of their service was associated in a higher proportion of infra-popliteal endovascular procedures (pre-service = 12.9%, service = 20.1%, P = .003).

Williams found no change in the annual mean number of open procedures performed (25.5 vs 24.3, pre-service to service, P = .83); however, insufficient data were reported to make this comparison for endovascular procedures.

3.7 | Mortality

Survival data were reported in three articles. Only Flores reported comparative 1-year mortality outcomes, with no significant difference in outcomes identified (pre-service = 6.7%, post-service = 7.3%, P = .9). Following adjustment for confounding, no difference in the risk of long-term mortality was identified (HR 1.10, 95% CI 0.78-1.55, P = .6).

Driver identified a significant improvement in overall mortality in favour of their limb salvage service (pre-service = 19.5%, service = 7.7%, P < .001); however, only patients with 3 years of follow-up were included. Alexandrescu reported an overall mortality rate of 9% at 12 months and 21% at 24 months across both cohorts, although no comparative data was provided.

3.8 | Wound healing

Vartanian reported complete wound healing was achieved in 59% of patients within their service by the end of their study (median follow-up 207 days). They reported a median time to healing of 12 (range 1-73) weeks; however, no comparative data was presented.

4 | DISCUSSION

Patients with CLTI/DFU represent a complex, multi-morbid group who at minimum require input from multiple specialities in order to receive effective care. While MDT services are established in the management of DFUs, they frequently provide limited access to thorough vascular assessment and treatments. Specialist vascular limb salvage services help build upon this MDT model to provide a more comprehensive service to patients.

This review highlights the limited number but wide variety of vascular limb salvage services which are present within the literature. In some cases, these services provided access to a wide array of specialist input from medical and allied health professionals, offering a comprehensive package of care to their patients.

The results of this review also demonstrate the encouraging outcomes of these services, as evidence by the reduction in published rates of major amputations. Interestingly, these services had different effects on individual centres in terms of the volume and nature of revascularisation procedures. While contradictory results for procedural volumes were reported, trends towards more challenging infra-popliteal procedures were identified, both potentially reflecting the increasing proportion of patients managed with DFU and/or complex arterial disease. Despite improvements in major amputation outcomes, data on mortality were conflicting and as such, drawing a conclusion on this outcome is not possible.

To date, this is the first review of its kind to investigate vascular limb salvage services in the management of CLTI/DFU. Two similar systematic reviews by Musuuza and Buggy both identified improvements in the rates of amputation when investigating the impact of MDT services in the management of DFUs. Buggy also identified a trend towards improved mortality, although this was not statistically significant. Both reviews however, utilised a broad definition of "MDT services" and did not investigate in the context of CLTI, issues which this systematic review aimed to address.

While this review provides tentative evidence to support the use of limb salvage services, it also exposes issues within the current literature. Developing quality evidence to support the use of these services is inherently difficult. For obvious reasons experimental studies are challenging and the heterogeneous nature of treatments and healthcare systems means studies are exclusively single centre in design. Indeed, the recommendations for the use of MDT services within the diabetic foot guidelines from the National Institute of Health and Care Excellence are based exclusively on "very low" quality evidence, as defined by the GRADE criteria. Furthermore, referral criteria of patients into individual limb salvage service may lead selection bias in favour of patients with intrinsically lower risk of amputation.

Even taking account of these challenges, systemic weaknesses are evident in the designs of the articles investigated. Five articles failed to provide sufficient baseline data to accurately define the population being studied and one failed to even provide a sample size. Furthermore, only six articles provided comparative institutional data, which is vital to validate the effectiveness of the described service.

The inclusion criteria and outcomes measures reported in a number of articles were also selective, leading to possible selection and reporting biases. Articles focussed predominantly on patients undergoing invasive intervention and some excluded patients requiring primary amputation altogether. Outcome measures also varied across studies, with no standardisation in the methodology of calculating major amputation rates or presentation of time-to-event data.

While future research is required to further validate these services, any research must address these concerns. At a minimum comparative data must be provided, along with sufficient baseline data to provide an accurate assessment of the population being treated. In line with suggestions from Jeffcoate and colleagues, this should include reporting details regarding comorbidities, the status of PAD and peripheral neuropathy, the nature of ulceration (if any) and the...
presence of infection. The use of the Society of Vascular Surgery WIfI (wound, ischaemia, foot infection) score provides a particularly useful tool in this context.\textsuperscript{32}

Based upon this review, it is also recommended that services present data on all patients diagnosed with CLTI/DFU, irrespective of their eventual treatment, as this helps to provide greater context to the operation of the service and minimises selection bias. In line with the recently published GVG, standardised definitions and reporting of outcome measures, including rate of major amputation, time to ulcer healing and mortality are also required, along with time-to-event data.\textsuperscript{3}

These changes (Table 4) would help not only to reduce bias but allow for greater pooling of data to provide high level evidence to evaluate the effectiveness of these services.\textsuperscript{31} Although these standards may be difficult to meet they should serve as an aspiration for future practice and bring about changes in how institutional data are collected.

### 4.1 Limitations

While this review is the first to examine the evidence for limb salvage service, it is not without limitation.

First, comparing outcomes before and after the inception of a limb salvage service, even on a single institutional level, is inherently difficult and carries potential for bias. As demonstrated in this review, many articles had highly selective inclusion criteria and some provided limited (or even no) baseline demographic data to allow for accurate comparison between groups. It is also possible that performance bias existed in the way patients were managed, with higher thresholds for amputations within limb salvage services. Likewise, publication bias may also exist, with the potential of services failing to publish outcomes which are not favourable. Although judging the exact effect of these biases is challenging, their potential means that the results of this review should be interpreted with some caution.

The heterogeneity between services also means the comparison of outcomes between institutions is unreliable. This issue limits the generalisability of the review’s conclusions as any benefits of limb salvage services may be specific to an individual population.

Furthermore, the GVG criteria used to define a vascular limb salvage service “centre of excellence” are broad and open to individual interpretation. While this review used the agreed international definition, in a number of cases it was difficult to establish the true nature of services from a publication alone and in some circumstances differentiating a well-run MDT from a limb salvage service was challenging. In some cases, articles were also excluded as they failed to provide sufficient detail on the nature of the input of vascular surgery. It is therefore plausible that services were incorrectly included or excluded from the review, although it is not possible to establish how this could have affected the results. Using other criteria could have potentially alleviated this issue; however, the intention of this systematic review was to utilise the most contemporary guidelines, as defined by the GVG.

Lastly, using a search strategy which included all articles from 1995 onwards is controversial and not without limitation. This historical limit was applied following preliminary searches, which identified a number of potentially suitable articles published in the 1990s (although following the full selection process, the earliest included paper in the review was from 1999). However, the GVG criteria used to define services are contemporary and may not be applicable to historical services. This is particularly relevant as the methods and processes of managing CLTI have changed over this period. Using a more recent time limit could have helped to mitigate this; however, as one of the review’s aims was to explore the nature of these services within the literature, it was felt the breadth provided by this criterion outweighed any limitation.

In conclusion, a limited number of specialist vascular limb salvage services have been described, all based around the “toe-and-flow” model of care. The results of this review indicate that the inception of these services is associated with a significant reduction in the rate of major amputation for patients with CLTI and/or DFUs; however, no significant changes in minor amputation or mortality rates were identified. Methodological problems exist in many of the included articles and further research should adopt a more standardised approach to study design and outcome reporting in order to improve the quality of evidence within the literature.

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| Study area | Key recommendations for improved reporting\textsuperscript{3,31} |
|------------|--------------------------------------------------|
| Population | Demographic details (ie, age, sex, ethnicity)     |
|            | Key comorbidities (eg, diabetes, ischaemic heart disease) |
|            | Use of medical therapy (rates of anti-platelet and lipid lowering medication use) |
|            | All patients with chronic limb-threatening ischaemia/diabetic foot ulceration within service—irrespective of eventual treatment strategy |
| Service    | Referral criteria to service                      |
|            | Comparative institutional data—prior to inception of service |
| Disease    | Severity of wound, ischaemia and infection (eg, SVS WIfI score [also providing objective risk of major amputation]) |
|            | Prevalence of neuropathy                          |
|            | Reporting of treatment strategies utilised (eg, endovascular revascularisation, primary major amputation) |
| Outcomes   | Freedom from major amputation (based upon total patients) at a minimum of 12 months—providing time-to-event data |
|            | Time to wound/ulcer healing                       |
|            | Rate of mortality at a minimum of 12 months      |
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SUPPORTING INFORMATION

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

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