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Non-surgical interventions for preventing contralateral tissue loss and amputation in dysvascular patients with a primary major lower limb amputation (Review)

De Siqueira J, Russell DA, Siddle HJ, Richards SH, McGinnis E

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[Intervention Review]

Non-surgical interventions for preventing contralateral tissue loss and amputation in dysvascular patients with a primary major lower limb amputation

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ABSTRACT

Rationale

Major lower limb amputation (LLA, above the ankle) is performed for people with intractable pain, life-threatening infections, or non-functional limbs. Of 7500 LLAs carried out in England between 2015 and 2018, the majority of these were performed in dysvascular patients. Dysvascularity is the absence of adequate blood supply to maintain a limb's usual function (ischaemia, usually caused by peripheral arterial disease or diabetes mellitus), ultimately leading to pain and tissue injury (ulcers, gangrene, sometimes referred to as tissue loss). Among those who undergo dysvascular LLA, 5.7% and 11.5% will likely undergo contralateral LLA at one and five years respectively, which is associated with greater disability and lower likelihood of returning to work, increasing the psychological burden to the patient and socioeconomic cost to the patient and health service. While extensive research has been carried out in the management of peripheral arterial disease and the care of diabetic feet, there are no guidelines for practice on prevention of contralateral amputation.

Objectives

To assess the effects of non-surgical interventions versus placebo, no intervention, or other non-surgical interventions on contralateral limb (CLL) tissue loss and amputation in dysvascular patients with a primary major LLA.

Search methods

The Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase, CINAHL and PEDro databases and the World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov trials registers until 20 March 2023. We also checked the references of identified studies and contacted study authors and manufacturers of relevant products.

Eligibility criteria

We aimed to include all randomised controlled trials (RCTs) and quasi-RCTs (e.g. randomised by birthdate) comparing the effectiveness of a non-surgical intervention with placebo, no intervention, or other non-surgical intervention, in adults with a primary major LLA due to dysvascularity. Interventions could be physical, pharmacological, educational, behavioural, or organisational, and delivered by a healthcare professional or carer.

Outcomes

Our critical and important outcomes of interest were as follows.

Critical outcomes

• Incidence of new localised tissue injury or ulceration (tissue loss) of the CLL, regardless of stage or classification at given time points.

• Time to the development of any localised tissue injury or ulceration (tissue loss) of the CLL, regardless of stage or classification.

• Incidence of new minor amputation (through the ankle, foot, or toe(s)) of the CLL at given time points.

• Time to new minor amputation (through the ankle, foot, or toe(s)) of the CLL.

• Incidence of new major amputation (whole limb or partial limb, above the ankle) of the CLL at given time points.

• Time to new major amputation (whole limb or partial limb, above the ankle) of the CLL.

Important outcomes

• Survival (time to death from all causes) at 12 months.

• Patient-reported outcome measures of health-related quality of life (HRQoL) using validated scales such as the 12-item Short Form Health Survey (SF-12) and EQ-5D.

• Adverse events (e.g. infections in the CLL).

• Hospital readmission.

Risk of bias

We used Cochrane's RoB 1 tool to assess risk of bias in the included study.

Synthesis methods

We were only able to perform a narrative review due to lack of data. We reported risk ratios (RR) with 95% CIs for dichotomous outcomes. We used GRADE to assess the certainty of evidence for each outcome.

Included studies

We found one eligible study, which compared electrostimulation of the gastrocnemius muscle and standard rehabilitation against standard rehabilitation in 50 dysvascular amputees.

Synthesis of results

There was no new incidence of tissue loss reported. The following outcomes were not reported: time to new tissue loss; time to and incidence of minor amputation; HRQoL outcomes; adverse events; and hospital readmissions. Electrostimulation was associated with a three-fold reduction in the incidence of new major amputation of the CLL (RR 0.33, 95% CI 0.04 to 2.99), although time to new major amputation was not reported. There was no difference between groups in 12-month survival (RR 1.0, 95% CI 0.85 to 1.18). We judged the overall certainty of the evidence (GRADE) as very low across all outcomes, with unclear risk of selection and detection bias and high risk of performance bias.

Authors' conclusions

Despite the care of the CLL being identified as a key research priority by two separate consensus papers, there is insufficient high-quality evidence to address this priority to date. We found only a single RCT suitable for inclusion, and this study was subject to risk of bias. Contralateral limb outcomes should be recorded in future research on dysvascular amputees. Until better evidence and clearer recommendations are available, this topic is likely to remain a research priority.

Funding

This Cochrane review had no dedicated funding.

Registration

Protocol available via DOI 10.1002/14651858.CD013857

PLAIN LANGUAGE SUMMARY

Are there any treatments to prevent harm to the remaining leg in people with amputations resulting from disorders of blood vessels?

Key messages

• There is not enough evidence to know if any treatment helps to reduce injury to the remaining leg in amputees.

• More research is needed into treatments to prevent harm to the remaining leg in this group.

Why are amputations of the leg performed?

Amputations of the leg are commonly performed due to problems with the blood supply of the leg, typically because of diabetes or problems with the circulation caused by older age, smoking, high blood pressure, and high cholesterol. This is commonly referred to as 'dysvascularity'. Approximately 1 in 10 people who have a leg amputated go on to lose the other leg.

Why is the remaining leg important in people who have amputations?

The care of the remaining limb has been identified as a key priority research area by groups of healthcare professionals and patients, in particular preventing further injury to the limb, including ulcers, gangrene (death of tissue due to an infection or lack of blood flow), and amputation. However, little is known regarding treatments (educational, medical, psychological, behavioural) that reduce the risk of losing the remaining limb in people who have had an amputation. These treatments may involve reducing pressure on the limb to prevent ulcers, or improving blood flow in the remaining limb with the use of medication, thus preventing further episodes of ulcers or gangrene which lead to limb loss.

What did we want to find out?

We wanted to know if any treatment other than surgery can help preserve and protect the remaining limb. These include medicines; educational toolkits, which may include books, leaflets, and online courses for patient participation; dressings, arrangements of care for people at home; and changes to how organisations deliver care.

What did we do?

We searched for studies comparing any non-surgical treatment with any other non-surgical treatment or no treatment for preserving and protecting the remaining limb in leg amputees. We included studies that reported on injuries such as ulcers and gangrene or amputation of the remaining limb. We aimed to compare and summarise the results and rate our confidence in the evidence based on factors such as study methods and sizes.

What did we find?

We included one study that compared electrical stimulation therapy to the calf of the remaining leg plus usual rehabilitation versus usual rehabilitation alone after surgery in 50 people who had an amputation. This is an experimental technique that has not been widely practised or written about. The study found no new incidence of tissue loss and no difference between groups in overall survival of people, but those who had undergone electrical stimulation therapy were three times less likely to have an amputation (4% versus 12%). The study did not report on time to new tissue loss, amputation, or minor amputation, or on the incidence of minor amputation.

What are the limitations of the evidence?

We found only a single study. There were problems with how the study was conducted and reported. Importantly, there was no difference in the appearance of ulcers or gangrene, or pain in the limbs of those who took part in the study, so it is not clear why there was a difference in the amputation rate. We therefore have little confidence in the available evidence. Further research is needed.

How up-to-date is this evidence?

The evidence is current to March 2023.

Summary of findings 1. Non-surgical interventions compared with standard care for preventing contralateral tissue injury or amputation

Non-surgical interventions compared with standard care for preventing contralateral tissue injury or amputation

Patient or population: adults who have had a primary major LLA due to dysvascularity

Settings: all care settings, including hospitals, community, and care homes

Intervention: non-surgical interventions[a]

Comparison: standard care[b]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care	Risk with non-surgical interventions				
Incidence tissue injury/ulceration (tissue loss) of the CLL 12 months	**Study population:** unilateral dysvascular amputees undergoing rehabilitation (standard care) ± electrical stimulation of gastrocnemius muscle (intervention)		-	50 (1)	⊕⊖⊖⊖ **Very low**[c]	The study authors reported no new tissue loss in either study arm. Due to the absence of any events, a RR cannot be calculated for this outcome.
	0 per 1000	**0 per 1000**				
Time to tissue injury/ulceration (tissue loss) of the CLL	See comment		-	-	-	This outcome was not reported, as there was no new localised tissue injury or ulceration.
Incidence of minor amputation of the CLL	See comment		-	-	-	This outcome was not reported.
Time to minor amputation of the CLL	See comment		-	-	-	This outcome was not reported.
Incidence of major amputation of the CLL 12 months	**Study population:** unilateral dysvascular amputees undergoing rehabilitation (standard care) ± electrical stimulation of gastrocnemius muscle (intervention)		**RR 0.33** (0.04 to 2.99)	50 (1)	⊕⊖⊖⊖ **Very low**[d]	
	120 per 1000 (100 to 140 per 1000)	**40 per 1000** (28 to 52 per 1000)				

Time to major amputation of the CLL	See comment	-	-	-	This outcome was not reported.
Survival 12 months	**Study population:** unilateral dysvascular amputees undergoing rehabilitation (standard care) ± electrical stimulation of gastrocnemius muscle (intervention)	**RR 1.0** (0.85 to 1.18)	50 (1)	⊕⊝⊝⊝ **Very low**[e]	In the single included study, 2 participants died in each study arm at 12 months' follow-up.
	908 per 1000 (889 to 927 per 1000) **908 per 1000** (889 to 927 per 1000)				

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **CLL:** contralateral limb; **LLA:** lower limb amputation; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Interventions delivered by any healthcare professional, including physical, pharmacological, educational, behavioural, or organisational. In this single study, the intervention was rehabilitation programme plus electrostimulation of gastrocnemius muscle (2 hours/day for 8 weeks). Biphasic charge balanced asymmetrical current stimuli with a pulse duration of 0.25 ms. Delivered in 4-second-long trains with a repetition rate of 40 Hz. Stimulation trains were rhythmically exchanged with pauses of the same duration. Amplitude was individually adjusted for each participant in order to achieve slight contractions of the gastrocnemius muscle (usually as 30 to 50 mA).
[b]Standard care is likely to include routine postoperative care and rehabilitation focusing on the primary LLA, without specific regard to the protection of the CLL. In this single study, standard care was a rehabilitation programme that included exercises for the muscles of the stump, exercises to improve balance, and walk training with prosthesis.
[c]Downgraded once for risk of bias (unclear risk of selection and detection bias, high risk of performance bias), once for imprecision (no measurable effect due to no events, single study), and once for indirectness (secondary, incidental outcomes).
[d]Downgraded once for risk of bias (unclear risk of selection and detection bias, high risk of performance bias), once for imprecision (large CIs), and once for indirectness (secondary, incidental outcomes).
[e]Downgraded once for risk of bias (unclear risk of selection and detection bias, high risk of performance bias), once for imprecision (large CIs), and once for indirectness (secondary, incidental outcomes).

BACKGROUND

Description of the condition

Major lower limb amputation (LLA) is a disabling operation carried out in people with limbs that are not salvageable to a functional state due to pain, loss of tissue, or life-threatening infection. It is defined as any amputation of the lower limb above the ankle (i.e. trans-tibial, through-knee, trans-femoral or hip disarticulation) [1]. Approximately 7500 LLAs were carried out in England between 2015 and 2018 [2]. Global estimates of incidence of amputation are difficult to establish given significant variability in reporting outcomes and measures [3]. The estimated cost to the United Kingdom's National Health Service is over GBP 60 million annually [4]. Studies assessing the quality of life scores of amputees reveal these to be significantly lower than those of the general population. Such differences are attributed to factors such as lack of employment, chronic pain, and limitations on mobility [5].

Amputation is occasionally performed in the management of traumatic limb injury and cancer, but is more common in the management of dysvascular patients (dysvascular amputation) [6]. 'Dysvascularity' refers to the absence of adequate blood supply to maintain a limb's usual function (ischaemia), ultimately leading to pain and tissue injury: breaks in the epithelial surface of the skin, which can penetrate to deeper tissues (ulceration), and necrosis or death of tissues (gangrene). These conditions are also included in the definition of chronic limb-threatening ischaemia. Dysvascularity, like ischaemia, may have one or more underlying causes, including atherosclerotic peripheral arterial disease (PAD), diabetic macro- and microvascular disease, small and large vessel vasculitides, vascular traumatic injury and acute embolic phenomena. Dysvascularity is generally a systemic state and will usually affect both lower limbs. People with diabetes are at particular risk of dysvascular amputation due to the presence of sensory and autonomic neuropathy, which puts them at risk of tissue injury (ulcers), which may in turn lead to life-threatening infections or limb non-function [7].

Among those who undergo dysvascular LLA, 5.7% and 11.5% will likely undergo contralateral LLA at one and five years, respectively [8], and 33% will die within three years [9]. Dysvascularity due to PAD and diabetes is an independent predictor of contralateral limb (CLL) loss. National Institute for Health and Care Excellence (NICE) guidance does not have specific advice regarding the prevention of LLA. However, there are two related guidelines: (NG19) Diabetic foot problems: prevention and management [10] found effectiveness for multidisciplinary teams for inpatients, clear protocols and pathways for a continued and integrated foot protection service, foot examination and certain foot orthoses, but no significant difference in effectiveness of patient education, augmented foot examination and other foot orthosis; (CG147) PAD: diagnosis and management [11] reports ulceration as a symptom of PAD; however, prevention was outside its remit. Additional searches for evidence of the effectiveness of interventions for primary LLA have found a paucity of studies. However, there is further evidence for the prevention of diabetic foot ulcers. For example, a Cochrane review of complex interventions for the prevention of diabetic foot ulcers found six low-quality studies that met their criteria, two of which had a significant reduction of foot ulceration or LLA or both [12], and a systematic review of footwear and offloading interventions found sufficient good-quality evidence to support the use of devices to prevent plantar/neuropathic foot ulcers, but very little evidence for all other foot ulcers (e.g. those associated with PAD) [13].

This review focused on secondary prevention of complications of the CLL following a first major LLA because, although we know indications for CLL loss are the same as for primary amputation (critical limb ischaemia), bilateral amputees require significantly more energy to mobilise and have much poorer functional status than do unilateral amputees [14]. Local audits have also shown that there is an exceptionally high risk of ulceration or LLA of the CLL or both; that care of the CLL is substandard; and patients have told us that while highly motivated to preserve the CLL, they receive little information/support, and the impact on quality of life, mortality, and healthcare costs greatly increase following amputation of the CLL.

Description of the intervention and how it might work

There is currently no accepted standard for the care of the CLL in unilateral amputees. Patients will not necessarily receive regular follow-up after LLA, particularly those who do not go on for prosthesis fitting. While a number of interventions already exist that are typically used in the prevention of primary amputation and the management of tissue injury in dysvascular patients, these are naturally also used in the prevention of contralateral tissue injury and limb loss.

Interventions for the prevention of limb loss may be:

- physical (e.g. offloading the foot [15], applying emollients [16]);
- pharmacological (e.g. prostanoids; antiplatelet [17] and cholesterol-lowering treatment for PAD [18]);
- educational (e.g. education of staff, patients, or carers in prevention strategies [19]);
- behavioural (e.g. motivating and refocusing patients following their primary LLA [20] to care for their CLL); and
- organisational (e.g. care pathways [21], audit standards that aim to improve outcomes for the CLL).

Pressure-offloading interventions aim to alter the biomechanics of gait and to reduce static pressure on the foot. They are typically used in the management of ulceration, as direct pressure is believed to contribute to the mechanical breakdown of skin and plantar fat, particularly in dysvascular patients with neuropathy and foot deformity. They have been shown to promote ulcer healing in two meta-analyses [22, 23]; by inference, they may affect (contralateral) limb loss, but the evidence for this is less established. Topical treatments (dressings, creams) for damaged or ulcerated skin are viewed as an important aspect of all ulcer management, irrespective of location or underlying aetiology. Protecting the skin from excess moisture, bacterial colonisation, and other deleterious factors should promote its normal functioning and healing [24, 25].

Pharmacological interventions modulate the pathological vascular biological state underlying dysvascularity. The presumed utility of their use in PAD is extrapolated from coronary disease and stroke [26, 27]. However, antiplatelet medication and cholesterol-lowering drugs have been demonstrated to stabilise atherosclerotic disease [28, 29]. By inference, they may prevent the evolution of a critically ischaemic state in the peripheral circulation.

Education of staff, patients, and carers aims to alert them to early and critical signs of limb-threatening dysvascularity [30]. Such education may bring about timely intervention to prevent further deterioration and limb loss. Behavioural interventions aim to modify patients' lifestyle decisions, including medication compliance and blood glucose control, which are established risk factors for the progression of disease [31]. Lastly, organisational interventions aim to improve patient pathways, reduce waiting times, and promote targeted review in order to alter outcomes [10].

Why it is important to do this review

Undergoing a bilateral amputation is associated with both poorer functional status and physical ability than that experienced by individuals who have had unilateral amputation [32]. However, there is a lack of clarity and paucity of evidence to suggest how to prevent patients from progressing from unilateral to bilateral amputation; the degree to which the effectiveness of interventions tested in primary prevention settings translate into improved outcomes in this group of patients is unknown. The need for this review was identified following an ongoing National Institute for Health Research (NIHR) Programme Grant for Applied Health Research (PGfAHR) application, a retrospective review of the care of patients following major limb amputation, and a consultation with a local patient group who highlighted a lack of advice and interventions for their CLL following major limb amputation. More recently, a Delphi consensus process [33] and a national (UK) research prioritisation process [34] have both identified the care of the CLL as a key priority for patients, carers, and clinicians. While the absence of known evidence was identified during both of these consensus processes, there has never been a published systematic review of the literature to address what the body of evidence demonstrates. However, given the recency of these consensus processes, it is unlikely that trials have been completed since their publication.

This review will likely benefit vascular surgeons, podiatrists, orthotists, nursing staff, physiotherapists, occupational therapists, and rehabilitation specialists who care for and manage dysvascular patients who have undergone a major LLA, as it will inform their practice. It will also benefit the patient population by aiding decision-making and improving the ability of their caregivers and healthcare teams to care for them effectively. We hope to benefit policymakers by identifying clinically effective interventions and directing future guidelines for the care of dysvascular patients. Finally, we hope to help researchers who may be able to design future trials informed by the results of this review.

OBJECTIVES

To assess the effects of non-surgical interventions versus placebo, no intervention, or other non-surgical interventions on contralateral limb tissue loss and amputation in dysvascular patients with a primary major lower limb amputation.

METHODS

We followed the Methodological Expectations for Cochrane Intervention Reviews (MECIR) when conducting the review [35], and PRISMA 2020 for reporting [36]. The lack of identified studies precluded a number of analyses. There were no cluster-randomised or cross-over trials, and no unit of analysis issues surrounding the reporting of limbs or lesions.

Where full outcome data were available, we planned to compare the effects using the best- and worst-case scenario as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* [37]; however, this was not possible given the absence of any available data. We planned to generate funnel plots and examine them for asymmetry to assess publication bias if more than 10 studies were included, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* [37]. We performed no meta-analysis, analysis of heterogeneity, subgroup analysis, or sensitivity analysis as planned in the protocol [38] due to the inclusion of only one study.

Criteria for considering studies for this review

Types of studies

We followed our previously published protocol [38]. We aimed to include all randomised controlled trials (RCTs) and quasi-RCTs (e.g. randomised by birthdate) that compared the effectiveness of a non-surgical intervention with placebo, no intervention, or other non-surgical intervention on the development of localised tissue injury in dysvascular patients undergoing a primary major LLA. Both individually and cluster-randomised studies were eligible for inclusion.

Types of participants

We included adults (18 years or older) who had a primary major LLA (as defined above [1]) due to dysvascularity, including atherosclerotic PAD, diabetic macro- and microvascular disease, and small and large vessel vasculitides. Participants must have been adults from the point of decision to have a primary major LLA. There were no restrictions on gender, race, or educational status, care setting (hospital, community, care home), or country. We excluded people who had a primary major LLA solely due to trauma, malignancy, or infections not associated with dysvascularity.

Types of interventions

We included any non-surgical intervention delivered by any healthcare worker, including doctors, nurses, physiotherapists, podiatrists, healthcare assistants, and carers, with the aim of preventing ulceration or amputation of the CLL. We included the following interventions:

- physical (e.g. offloading the foot [15], applying emollients [16]);
- pharmacological (e.g. prostanoids; antiplatelet [17] and cholesterol-lowering treatment for PAD [18]);
- educational (e.g. education of staff, patients, or carers in prevention strategies [19]);
- behavioural (e.g. motivating and refocusing patients following their primary LLA [20] to care for their CLL); and
- organisational (e.g. care pathways [21], audit standards that aim to improve outcomes for the CLL).

Interventions could have been delivered:

- as a 'one-time', 'repeated', or 'ongoing' intervention;
- at the time of the primary major LLA or any time following;
- singularly or as part of a complex intervention package.

We also aimed to identify and report on any measures of adherence or compliance with interventions and their findings.

Any of the following comparisons were eligible for inclusion.

- Non-surgical intervention (physical, pharmacological, educational, behavioural, or organisational) versus placebo.
- Non-surgical intervention (physical, pharmacological, educational, behavioural, or organisational) versus no intervention.
- Non-surgical intervention (physical, pharmacological, educational, behavioural, or organisational) versus standard care.
- Non-surgical intervention (physical, pharmacological, educational, behavioural, or organisational) versus non-surgical intervention (physical, pharmacological, educational, behavioural, or organisational).

As there is no accepted 'standard care' for the CLL, our initial categorisation was based on study authors' reports. If we later identified overlap between intervention categories and comparators, we would re-categorise this information.

Outcome measures

As this review aimed to identify interventions that lead to particular outcomes, we only included studies that reported on at least one of our outcomes of interest.

Critical outcomes

- Incidence of new localised tissue injury or ulceration (tissue loss) of the CLL, regardless of stage or classification at given time points.
- Time to the development of any localised tissue injury or ulceration (tissue loss) of the CLL, regardless of stage or classification.
- Incidence of new minor amputation (through the ankle, foot, or toe(s)) [1] of the CLL at given time points.
- Time to new minor amputation (through the ankle, foot, or toe(s)) [1] of the CLL.
- Incidence of new major amputation (whole limb or partial limb, above the ankle) [1] of the CLL at given time points.
- Time to new major amputation (whole limb or partial limb, above the ankle) [1] of the CLL.

Important outcomes

- Survival (time to death from all causes) at 12 months.
- Patient-reported outcome measures of health-related quality of life (HRQoL) using validated scales such as the 12-item Short Form Health Survey (SF-12) [39] and EQ-5D [40].
- Adverse events (e.g. infections in the CLL).
- Hospital readmission.

We planned to record the latest time point given for study follow-up and 12 months post-primary major LLA, but we could have been guided by the time points used in the individual studies. The review authors agreed that if other clinically important outcomes were measured, we would consider these for inclusion.

Search methods for identification of studies

Electronic searches

The Cochrane Vascular Information Specialist conducted systematic searches of the following databases for RCTs without language, publication year, or publication status restrictions to 20 March 2023:

- Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web; searched 20 March 2023);
- Cochrane Central Register of Controlled Trials (CENTRAL; Issue 2, 2023, searched 20 March 2023) via the Cochrane Register of Studies Online (CRSO, searched 20 March 2023);
- MEDLINE Ovid (MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE (1946 to 20 March 2023);
- Embase Ovid (1974 to 20 March 2023);
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature) (1982 to 20 March 2023);
- PEDro (Physiotherapy Evidence Database) (searched 20 March 2023).

We also searched the following trial registries on 20 March 2023.

- ClinicalTrials.gov (clinicaltrials.gov).
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (www.who.int/clinical-trials-registry-platform).

We developed search strategies for other databases based on the search strategy designed for MEDLINE. Where appropriate, the strategies were combined with adaptations of the Highly Sensitive Search Strategy designed by Cochrane for identifying RCTs and controlled clinical trials (as described in Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* [41]). Search strategies for major databases are provided in Supplementary material 1.

Searching other resources

We examined the bibliographies of all studies identified for references to other relevant studies. We contacted specialists in the field and manufacturers of dressings, offloading devices (e.g. Smith and Nephew, Coloplast, ConvaTec, Molnlycke, Urgo Medical, Frontier Medical Group, DM Systems, Posey, Covidien, Sundance Solutions, Anatomical Concepts Inc, Promedics, Streifeneder, Ossur, Steeper), and drugs (Bristol Myers Squibb, Bayer, AstraZeneca, Pfizer), and authors of included studies for any unpublished data that reported at least one of our critical outcomes.

Data collection and analysis

Selection of studies

We used Cochrane's Screen4Me workflow to help assess the search results. Screen4Me comprises three components: known assessments - a service that matches records in the search results to records that have already been screened in Cochrane Crowd and been labelled as an RCT or as Not an RCT; the RCT classifier - a machine learning model that distinguishes RCTs from non-RCTs; and if appropriate, Cochrane Crowd - Cochrane's citizen science platform where the Crowd help to

identify and describe health evidence. For more information about Screen4Me and the evaluations that have been done, visit the Screen4Me webpage on the Cochrane Information Specialists portal: community.cochrane.org/organizational-info/resources/resources groups/information-specialists-portal.

Two review authors (JD, EM) independently screened the titles and abstracts identified by the searches for potential relevance. We retrieved the full-text reports of all studies deemed potentially relevant, and the same two review authors independently assessed the full-text studies for inclusion in the review. Another review author (DR) was consulted where there was disagreement. We listed all articles that appeared at first to meet the inclusion criteria but that on closer review of the full text did not in the 'Characteristics of excluded studies' table along with their reasons for their exclusion.

We illustrated the study selection process in a PRISMA flow diagram [42].

Data extraction and management

Two review authors (JD, EM) independently extracted and recorded data on the piloted data collection form. Another review author (DR) was available to arbitrate in cases of disagreement, but this was not necessary. We collected the following information: study publication details, design, details of population, inclusion and exclusion criteria, intervention, numbers of participants in each group, duration of treatment and follow-up, outcomes, and adverse events.

Risk of bias assessment in included studies

Two review authors (JD, EM) independently assessed risk of bias in the included studies in accordance with the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* [43], and presented the results in a risk of bias table. Another review author (DR) was available to arbitrate in cases of disagreement; however, none occurred. We planned to contact study authors if clarification was needed to better assess the risk of bias, though this was not necessary. Had we identified any cluster-RCTs, we would have examined these for risk of bias due to recruitment bias, baseline imbalance, loss of clusters, incorrect analysis and comparability with individually randomised controlled trials [44].

Measures of treatment effect

We planned to report hazard ratios (HR) with 95% confidence intervals (CIs) if studies reported time-to-event (and survival) outcomes. We used the risk ratio (RR) with 95% CIs for studies with dichotomous outcomes such as incidence or number of events at a given time.

Unit of analysis issues

The unit of analysis was the participant.

Dealing with missing data

We contacted the study authors to retrieve any missing data. Where response was not adequate, we considered the available data and the impact of the missing data on risk of bias. However, data retrieved from authors was insufficient to enable inclusion of the trials in the review. Where possible, we conducted analysis on an intention-to-treat (ITT) basis.

Reporting bias assessment

We did not have sufficient studies (n = 10) to generate funnel plots and examine them for asymmetry to assess publication bias, as planned in our protocol, and as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* [37].

Synthesis methods

We presented a narrative review of the included study. We used a fixed-effect model in Review Manager 5 to synthesise all the data [45]. For dichotomous outcomes (relating to clinical events), we used the RR with 95% CI. We planned to use HR with 95% CI if time-to-event outcomes were reported.

Investigation of heterogeneity and subgroup analysis

We considered clinical and statistical heterogeneity between studies. Given the broad scope of the review, clinical variability in interventions and outcomes was likely, and where appropriate, were to be presented and analysed separately. We planned to assess statistical heterogeneity using the Chi^2 test with a significance of $P < 0.10$ and the I^2 statistic. An I^2 statistic value greater than 50% may indicate substantial heterogeneity; in such cases we planned to pool results using a random-effects model. For values of I^2 less than 50%, we would pool results using a fixed-effect model. In the case of considerable heterogeneity (I^2 of 75% to 100%), we planned to report results narratively [37].

We planned to investigate the following subgroups; however, these analyses were precluded by insufficient data.

- Diabetes versus no diabetes
- Effect of level of primary limb amputation (above knee amputation (AKA) versus through or below knee amputation (TBKA))
- Ambulatory status (walking with prothesis or ambulatory aid versus restricted to chair/wheelchair/bed)

Equity-related assessment

We did not investigate health inequity in this review.

Sensitivity analysis

We planned to perform a sensitivity analysis excluding trials deemed to be at high risk of bias (i.e. more than two domains at high risk). We did not perform a sensitivity analysis as only one study was included.

Certainty of the evidence assessment

We prepared Summary of findings 1 to present the key information from the review. We used GRADEpro GDT software to create the table [46] for the comparison: non-surgical interventions compared with standard care for preventing contralateral tissue injury or amputation. We considered standard care to be the most important comparator for inclusion in Summary of findings 1 given that all amputees would normally receive some form of care regarding postoperative follow-up, medicine optimisation, and rehabilitation, making no intervention and placebo unlikely to be commonly used.

We included the outcomes described in Outcome measures at 12 months. We identified the seven most clinically relevant outcomes as incidence of new localised tissue injury or ulceration; time to

development of any localised tissue injury or ulceration; incidence of new minor amputation of the CLL; time to new minor amputation of the CLL; incidence of new major amputation of the CLL; time to new major amputation of the CLL; and survival.

Two review authors (JD, EM) assessed the certainty of the evidence for each outcome using the GRADE approach [47]. We judged the certainty of the evidence as high, moderate, low, or very low based on the five GRADE criteria (risk of bias, inconsistency, indirectness, imprecision, and publication bias). Another review author (DR) was available to arbitrate in cases of disagreement; however, none occurred.

Consumer involvement

There was no direct consumer involvement in this review due to limited resources. However, the outcomes of this review relate directly to national (UK) patient- and carer-identified priorities, as defined in another publication [34].

RESULTS

Description of studies

Results of the search

See Figure 1 for details of the search results.

Figure 1. PRISMA flow diagram, searches performed in March 2021, April 2022, and March 2023.

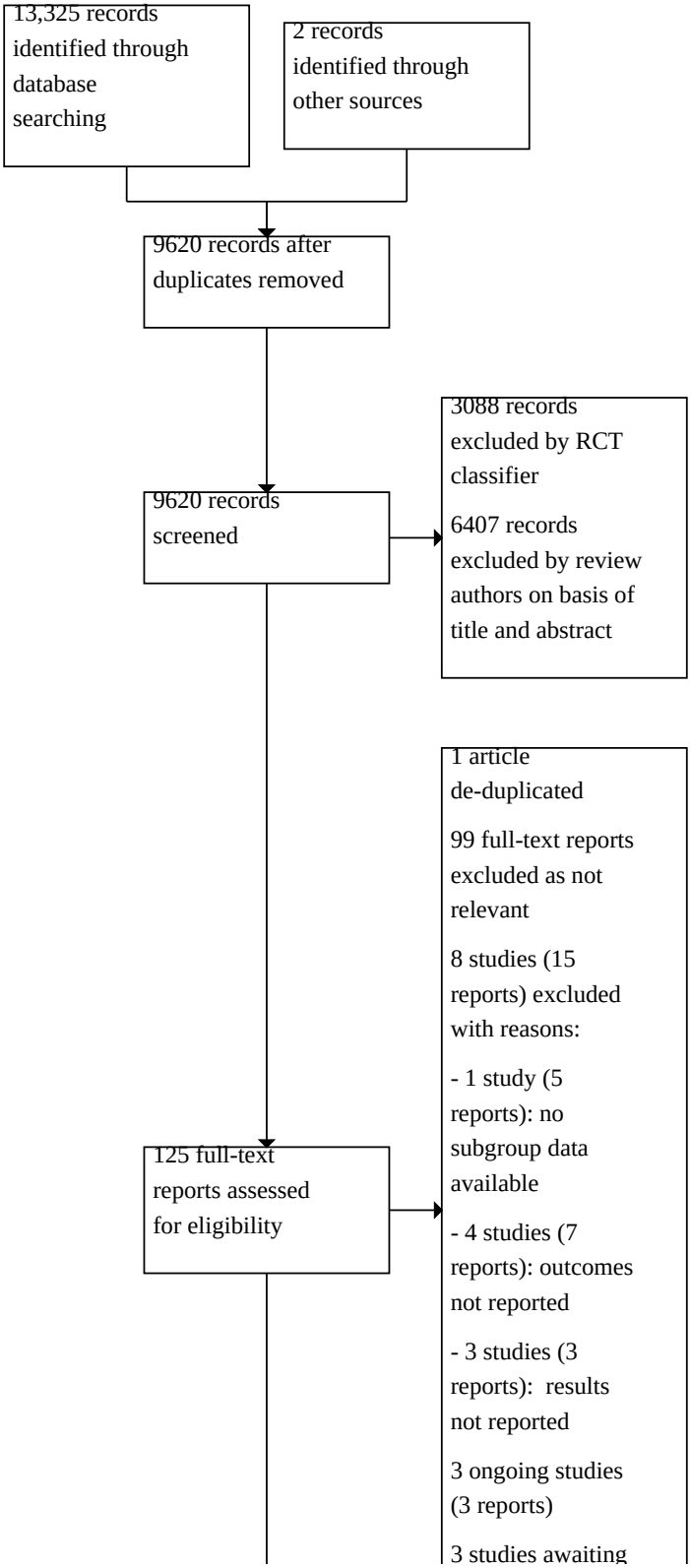
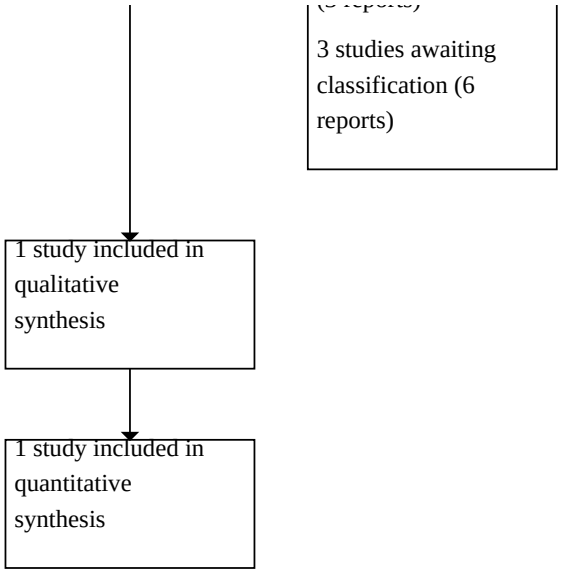


Figure 1. (Continued)



Our database searches identified 13,325 results, and we found two further studies through citation searches. After de-duplication, we used Cochrane's Screen4Me workflow to screen 8590 records of the remaining 9620 [48], to help identify potential reports of RCTs. The results of the Screen4Me assessment process are shown in Figure 2 and Figure 3. We then assessed the remaining 6532 records (5502 identified from Screen4Me plus an additional 1030 records from the top-up search that had not been put through Screen4Me) by title and abstract, excluding 6407 as not relevant. We assessed 125 potentially relevant reports in full text, of which 99 were identified as not relevant and one was a duplicate and were therefore excluded. We identified three ongoing studies (NCT03995238 [49]; NCT04083456 [50]; NCT05728411 [51]). We performed a detailed review of the remaining 22 reports. Of these, we identified one included study (Prešern-Štrukelj 2002 [52]), assessed three studies (six full-text reports) as awaiting classification (Long 2020 [53, 54, 55]; Nault 2019 [56, 57]; Rajamani 2011 [58]), and excluded a further eight studies (15 full-text reports) with reasons (Colwell 1984 [59, 60, 61, 62, 63]; Elessawy 2021 [64]; Ganguly 2008 [65]; Godlwana 2020 [66, 67]; Mazari 2010 [68]; NCT02054416 [69]; NCT02496351 [70]; Snyder 2018 [71, 72, 73]).

Figure 2. Screen4Me flow diagram 2021.

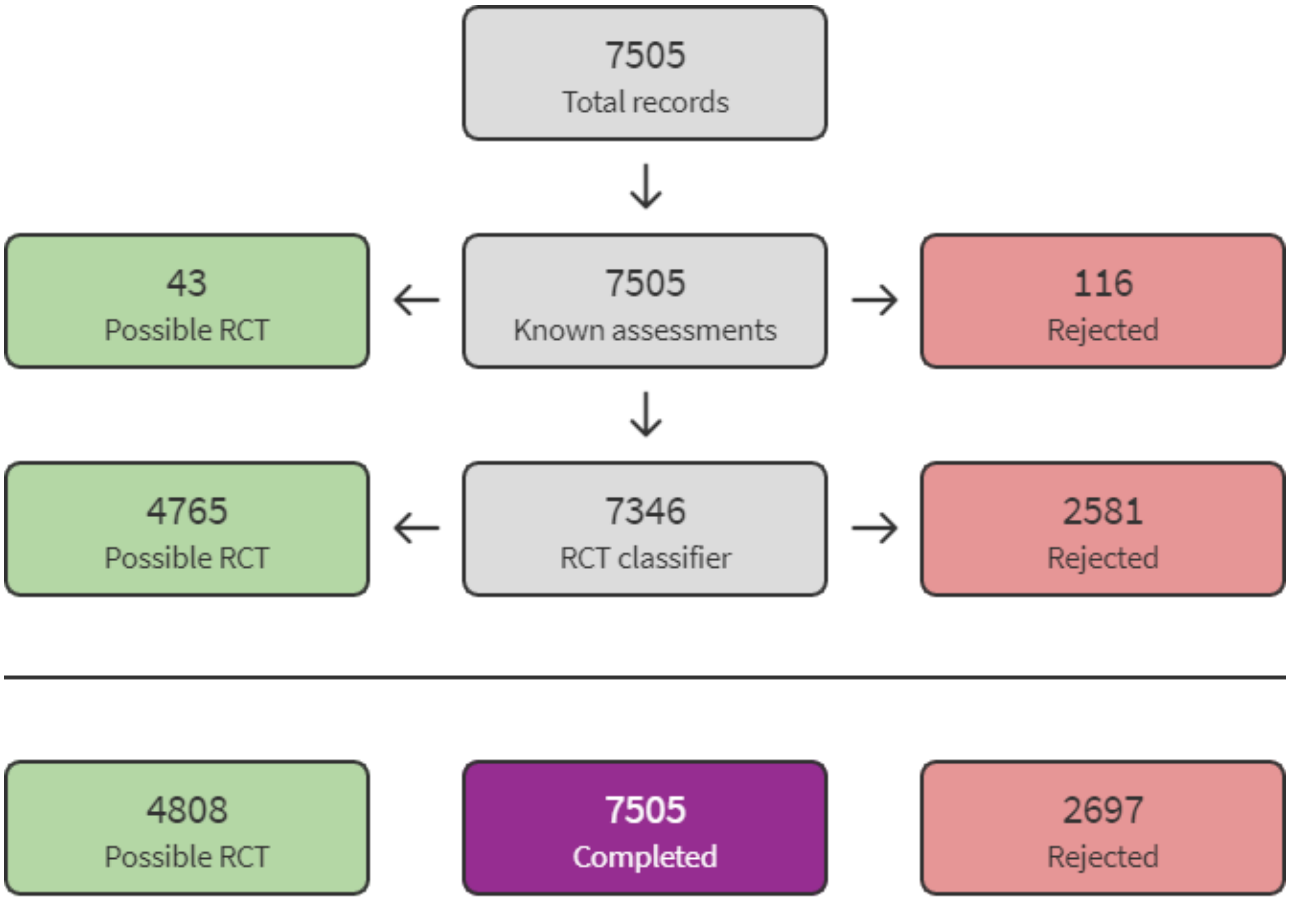
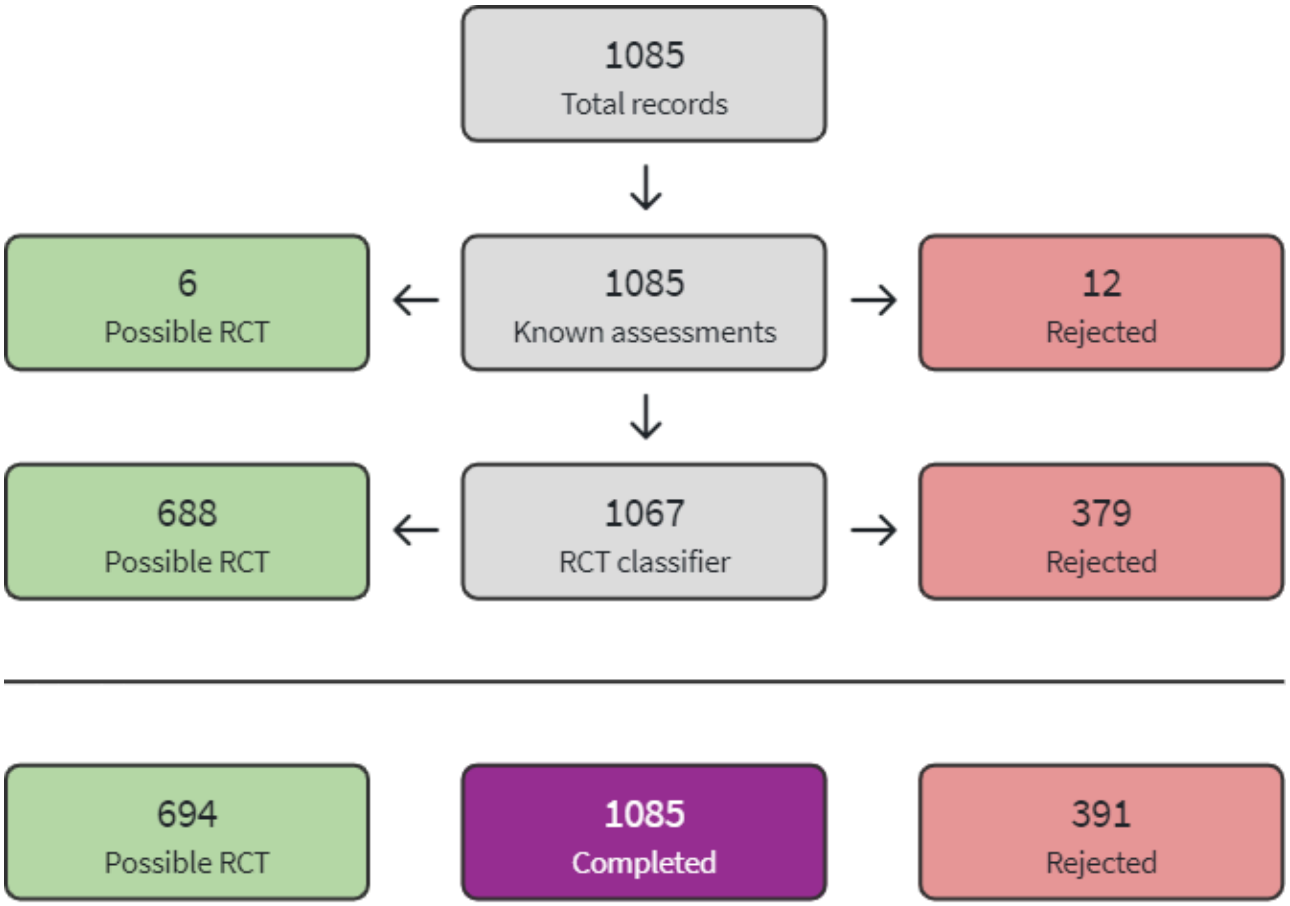


Figure 3. Screen4Me flow diagram 2022.



Included studies

A single study met the inclusion criteria (Prešern-Štrukelj 2002). This study compared a standard rehabilitation programme plus electrostimulation of gastrocnemius muscle (two hours/day for eight weeks) of the CLL against standard rehabilitation alone in 50 dysvascular amputees attending a postoperative rehabilitation programme in Ljubljana, Slovenia. The standard rehabilitation programme included exercises for the muscles of the stump, exercises to improve balance, and walking training with prosthesis. In addition to incidence of CLL amputation at the end of the programme, the study captured Fontaine Limb Classification (i.e. new tissue loss) in the CLL, ankle brachial index (ABI), tissue oxygenation, and biochemical parameters (haematocrit, cholesterol, and fibrinogen concentration) at eight weeks and one year. The funding source for this study was not stated. It is noteworthy that the outcomes of interest of this review were not part of the aim of the included study and may have been reported as incidental findings, particularly as there was no evidence of powering to detect these outcomes.

Study groups were reportedly well-matched, but the criteria by which this was judged were limited to only eight parameters (age, sex, level of amputation, diabetes mellitus, cholesterol, fibrinogen, blood pressure, and smoking). We made no attempt to contact the authors of this study as all necessary information was reported in the paper.

See Supplementary material 2.

Excluded studies

We excluded 115 reports following full-text assessment. We have reported the reasons for exclusion of eight of these studies (15 reports) below and in the 'Characteristics of excluded studies' table (See Supplementary material 3).

- One study: no subgroup data were available, thereby precluding eligibility. We contacted the authors for this information, but the data were not available for sharing (Colwell 1984).
- Four studies: outcomes of interest not reported (information sought from authors but no reply received) (Elessawy 2021; Godlwana 2020; Mazari 2010; Snyder 2018).
- Three studies: results not reported (information sought from authors but no reply received). One registered trial examined the use of an intermittent compression device in the remaining limb of dysvascular amputees and was expected to be completed in 2019; however, no results were published, and we received no response on contacting the authors (NCT02054416). A second registered trial investigated the use of transcutaneous electrical nerve stimulation. No results were published despite a planned recruitment end date of 2017. The authors were not contactable (NCT02496351). Lastly, one study assessed the use of non-contact casting in healing diabetic foot ulcers. We attempted to establish whether there may have been a small cohort of

patients who were already unilateral amputees and met our inclusion criteria, but there were no retrievable full texts of this paper, and we received no response from the publisher or author (Ganguly 2008).

Studies awaiting classification

Three studies included subpopulations that met our inclusion criteria and reported on an outcome of interest. We contacted the authors of these studies to request subpopulation data. Unfortunately, either the data were not available, or the authors did not reply to our communication. These studies have been described in the tables in Supplementary material 4 (Long 2020; Nault 2019; Rajamani 2011). Notably, all three of these studies assessed pharmacological therapy.

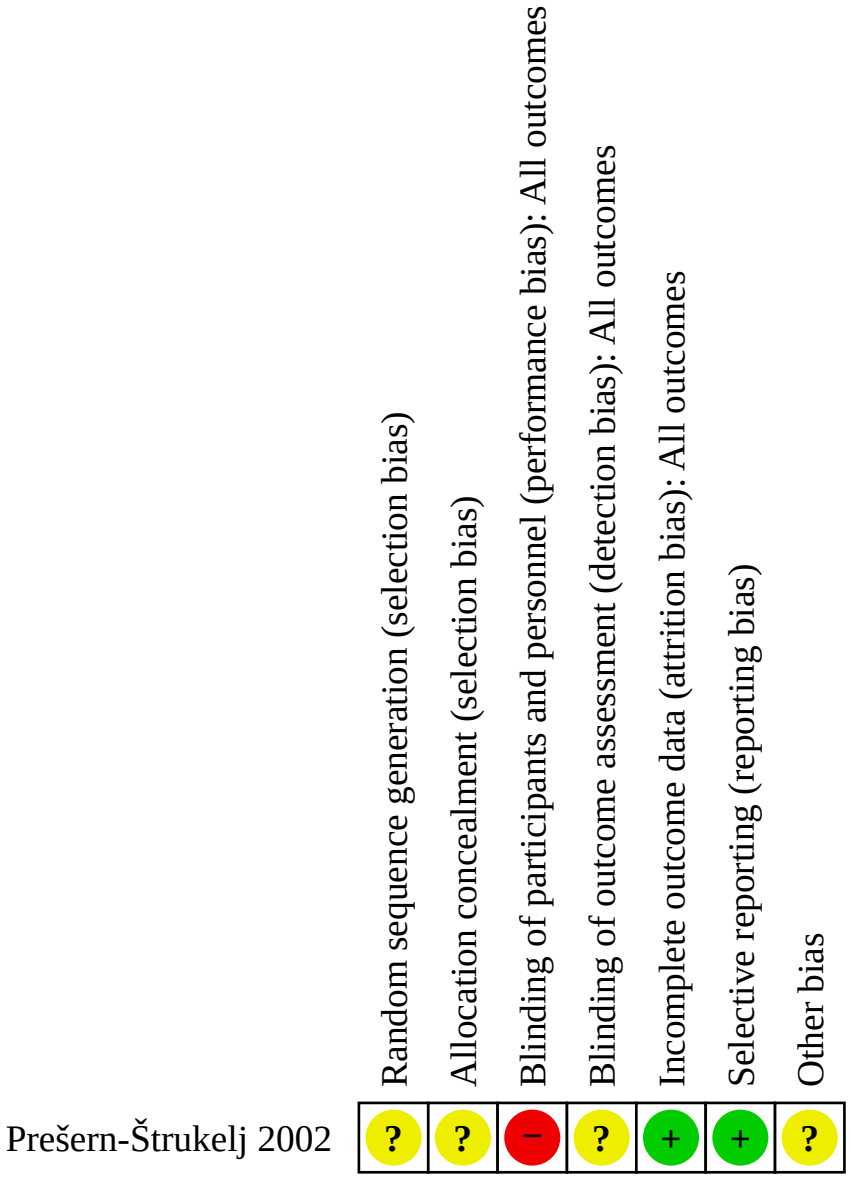
Ongoing studies

We identified three clinical trials assessing physical rehabilitation that appear to meet our inclusion criteria; however, results are not yet available (see Supplementary material 5) (NCT03995238; NCT04083456; NCT05728411).

Risk of bias in included studies

We included a single study that we judged to be at overall high risk of bias (Prešern-Štrukelj 2002). See Figure 4 for a summary of the risk of bias judgements.

Figure 4. Risk of bias summary.



The study did not describe how randomisation was achieved, resulting in a judgement of unclear risk of bias.

There was no mention of allocation concealment, resulting in a judgement of unclear risk of bias.

Due to the nature of the intervention, participants and those delivering the intervention could not be blinded, so we judged the included study to be at high risk of performance bias.

There was no mention of blinding of outcome assessors, resulting in a judgement of unclear risk of detection bias.

We assessed the included study as at low risk of attrition bias. All participants completed their allocated treatment, and there was no loss to follow-up.

We assessed the included study as at low risk of reporting bias. All outcomes were fully reported.

This study classified ischaemic by the Fontaine classification (i.e. not Rutherford). It is unclear how the Fontaine classification was recorded and reported both in the description of the patient population and in the outcome assessment, so we judged the included study to be at unclear risk of other bias.

Synthesis of results

Only one study with 50 participants met our inclusion criteria (Prešern-Štrukelj 2002).

We were unable to carry out any meta-analysis and have reported the results narratively below. These are presented in Summary of findings 1. A complete record of all comparisons and analysis is available for this review in Supplementary material 6, and a full data package is available in Supplementary material 7.

Critical outcomes

Incidence of new localised tissue injury or ulceration (tissue loss) of the CLL

The study authors did not report any new tissue loss in either arm of the study at eight weeks or one year. Therefore, there was no relative effect in either direction. See Supplementary material 6. The certainty of the evidence was very low. Electrostimulation of the gastrocnemius muscle may have little to no effect on this outcome, but the evidence is very uncertain.

Time to development of any localised tissue injury or ulceration (tissue loss) of the CLL

This was not reported, as there was no new localised tissue injury or ulceration.

Incidence of new minor amputation (through the ankle, foot, or toe(s)) of the CLL

This was not reported in the included study.

Time to new minor amputation (through the ankle, foot, or toe(s)) of the CLL

This was not reported in the included study.

Incidence of new major amputation (whole limb or partial limb, above the ankle) of the CLL

The authors described a CLL amputation rate of 3/25 in the control group and 1/25 in the experimental group. From the reported data, we calculated a risk ratio (RR) of 0.33 (95% confidence interval (CI) 0.04 to 2.99), favouring the experimental group. However, the wide CI also indicates the possibility of no effect. See Supplementary material 6. The certainty of the evidence was very low. Electrostimulation of the gastrocnemius muscle may have little to no effect on this outcome, but the evidence is very uncertain.

Time to new major amputation (whole limb or partial limb, above the ankle) of the CLL

Time to new major amputation was not reported in the included study, and it was not possible to calculate from the data provided.

Important outcomes

Survival (time to death from all causes)

At the end of the observation period of one year, four participants had died, two in each group. As no time-to-event data were reported, we assessed this as a dichotomous outcome, by means of RR. From the reported data, we calculated a RR of 1.0 (95% CI 0.85 to 1.18), demonstrating no treatment effect in either direction. See Supplementary material 6. The certainty of the evidence was very low. Electrostimulation of the gastrocnemius muscle may have little to no effect on this outcome, but the evidence is very uncertain.

Patient-reported outcome measures of health-related quality of life (HRQoL)

This was not reported in the included study.

Adverse events

This was not reported in the included study.

Hospital readmission

This was not reported in the included study.

DISCUSSION

Summary of main results

We included a single study involving 50 lower limb amputees that compared electromuscular stimulation and standard rehabilitation of the CLL with standard rehabilitation of the CLL alone (Summary of findings 1) (Prešern-Štrukelj 2002). Of our critical outcomes of interest, the included study reported on incidence of contralateral tissue loss (described according to the Fontaine classification), limb loss, and overall survival at 12 months. The study did not report on time to any events or incidence of minor amputations. No new tissue loss was reported in either treatment group, and there was an equal number of deaths. The study reported fewer amputations in the CLL in the electromuscular group, but this result should be interpreted with caution as the evidence is of very low certainty. Further, these outcomes were not part of the aim of the included study and may have been reported as incidental findings, particularly as there was no evidence of powering to detect them. We can draw no conclusions from these results.

We identified additional studies that included amputees in their population and recorded limb outcomes (Long 2020; Nault 2019; Rajamani 2011). However, upon contact with the authors, it was not possible to retrieve the data on this subpopulation from these studies to permit their inclusion in the review. These studies analysed the incidence of CLL loss and may have added to the results of this review. This represents a lost opportunity to consolidate knowledge in the care of this patient group. We hope we will be able to include this information in the review should it be made available in the future.

Limitations of the evidence included in the review

We assessed the overall certainty of the evidence in this review as very low. Electrostimulation during rehabilitation may reduce the incidence of CLL amputation, but the evidence is very uncertain. There were substantial vulnerabilities to bias in the single included study, and there was no power calculation in the

study, suggesting that the outcomes may have been found by chance. We downgraded the certainty in the evidence for tissue loss, amputation, and survival from high to very low due to risk of bias (unclear risk of selection and detection bias and high risk of performance bias), imprecision (no measurable effect due to no events, or large CIs, single study), and indirectness (secondary, incidental outcomes).

The evidence in this review comes from a single-centre RCT with few participants, implementing an uncommon and experimental technique. The use of neuromuscular stimulation is described in other rehabilitation studies [74]; however, this has mostly focused on the preservation of muscular strength in the amputated limb [75], rather than functionally improving or preserving the CLL. The absence of any demonstrable mechanism by which electrostimulation may aid limb preservation brings its validity as a limb preservation intervention into question. The intervention identified in this review can be considered experimental, rather than one which is widely adopted in clinical practice. The trial had substantial vulnerability to bias, and its results must be interpreted in this context. Our initial review question has not been answered by the evidence found in this review; it is unlikely that the single study with its limitations will be used to inform clinical practice.

The inclusion criteria for this review were relatively broad insofar as they included any non-surgical intervention that affects CLL outcomes. However, despite this, no interventions in offloading, physical therapy, or education were identified. Although we identified three large pharmacological studies, none of these had available data regarding outcomes in dysvascular amputees that could be analysed. Such large, well-conducted RCTs may have impacted the conclusions drawn from this review, if relevant outcomes had been included.

Of note, outcomes in the rehabilitation literature focused primarily on quality of life and return to functional status among amputees. While important outcomes in their own right, there is evidently a missed opportunity in the published literature to capture the key outcome of interest in this review. There may be data within these studies that could be analysed but are not evident in the published reports of these studies.

The outcome of the CLL has been identified as a key priority by the James Lind Alliance and by a separate Delphi paper on core outcome sets in amputation [34, 33]. Even if collected, the absence of reporting of this outcome raises an important question as to what degree the CLL is being valued and prioritised both by researchers and clinicians.

Limitations of the review processes

While this review followed a pre-established protocol [38] and guidance set out within the *Cochrane Handbook for Systematic Reviews of Interventions*, one potential source of bias has been a focus on outcomes, rather than interventions. While there may be a number of benefits to different interventions that did not report on an outcome of interest, we have not reported them. Further, CLL outcomes may have been included in a number of studies as secondary endpoints. Such outcomes may not have been mentioned in their published abstracts, and thus relevant papers may have been excluded on abstract review.

Additionally, it is not possible to rule out publication bias in the included literature. We excluded some studies because, while a published abstract had been identified, no corresponding full text was available, and it was not possible to ascertain from the abstract whether it met our inclusion criteria. Such abstracts also had no data that could be extracted.

Finally, the search date may be viewed as a limitation; however, we checked all ongoing studies and studies awaiting classification prior to publication, and their status remains unchanged. We therefore consider that all relevant studies have been included in the review, and that the evidence is current.

Agreements and disagreements with other studies or reviews

There are no other reviews in this field, therefore no comparisons can be drawn.

AUTHORS' CONCLUSIONS

Implications for practice

There is a lack of evidence for non-surgical interventions for preventing contralateral tissue loss and amputation in dysvascular amputees. Evidence regarding specific management of unilateral dysvascular amputees is very uncertain, and we cannot draw any conclusions from the one study included in this review. In the absence of stronger evidence, we cannot comment on any implications for practice.

Implications for research

Despite the outcome of the remaining limb being identified as a key priority area for amputation research by two separate consensus processes [33, 34], there is a substantial lack of evidence in this field. This review highlights the need for more research on the outcomes of the contralateral limb.

We identified a few studies that recruited amputees and recorded limb outcomes. However, it was not possible to retrieve the data from these studies in order to perform a subgroup analysis. This represents a lost opportunity to consolidate knowledge in the care of this patient group. These studies have been grouped as awaiting classification, and perhaps these data may become available in the future.

FInally, given the high priority allocated to this by consensus processes, future research involving amputees should include data collection on contralateral limb outcomes such as incidence of new tissue damage, infections and other complications or limb loss, even if this is not the primary target of the intervention. There is a need for studies that compare the addition of a contralateral limb health promotion activity to standard care alone, particularly around the time of their first amputation, when patients are likely to be more receptive to behaviour change to preserve their remaining limb.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD013857.

Supplementary material 1 Search strategies

Supplementary material 2 Characteristics of included studies

Supplementary material 3 Characteristics of excluded studies

Supplementary material 4 Characteristics of studies awaiting classification

Supplementary material 5 Characteristics of ongoing studies

Supplementary material 6 Analyses

Supplementary material 7 Data package

ADDITIONAL INFORMATION

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Editorial and peer-reviewer contributions

Cochrane Vascular supported the authors in the development of this intervention review.

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Stewart Walsh, Department of Surgery, National University of Ireland Galway;
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Joanne Duffield, Cochrane Central Editorial Service;
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments, and supported the editorial team): Sara Hales-Brittain, Cochrane Central Editorial Service;
- Copy Editor (copy editing and production): Lisa Winer, Cochrane Central Production Service;
- Peer reviewers (provided comments and recommended an editorial decision): Hosna Khazaei, Pharmacy student (consumer review); Nuala Livingstone, Cochrane Evidence Production and Methods Directorate (methods review); Jo Platt, Central Editorial Information Specialist (search review). Two additional peer reviewers provided clinical/content peer review but chose not to be publicly acknowledged.

Contributions of authors

JD: protocol drafting, acquiring trial reports, trial selection, searching of other sources, data extraction, data analysis, data interpretation, risk of bias assessment, GRADE assessment, review drafting, and future review updates.

DR: conception of the review, protocol drafting, arbitration in case of disagreements regarding decisions related to eligibility, data extraction, data interpretation, review drafting, and future review updates.

HS: conception of the review, protocol drafting, data interpretation, review drafting, and future review updates.

SR: conception of the review, protocol drafting, data interpretation, review drafting, and future review updates.

EM: conception of the review, design of the review, co-ordination of the review, protocol drafting, acquiring trial reports, trial selection, searching of other sources, data extraction, data analysis, data interpretation, risk of bias assessment, GRADE assessment, review drafting, future review updates, and guarantor of the review.

Declarations of interest

JDS: works as a Vascular Surgeon at Leeds Teaching Hospitals (LTH), UK. JDS was a member of the Vascular Society of Great Britain and Ireland's Research Committee at the time of the review. Neither LTH nor the VSGBI have a position on the topic of this review. JDS was a recipient of a personal award from the National Institute of Health Research (NIHR) at the time of the writing of the review. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR, University of Leeds, NHS, or the UK Department of Health and Social Care.

DAR: works as a Consultant Vascular Surgeon at Leeds Teaching Hospitals NHS Trust. DAR declares that his institution has received payments from URGO Medical and Integra Lifesciences (for membership of Diabetic Foot Advisory Board) and from URGO Medical (for his role as conference session chair and lectures on management of chronic wounds and diabetic foot ulcers). DAR is a recipient of a personal Advanced Fellowship award from the National Institute of Health Research Academy (NIHR300633). DAR has also declared that he is involved in a number of studies, as Chief Investigator (NIHR HTA Multiple interventions for diabetic foot ulcer treatment; NIHR HTA 15/08/77), Principal Applicant (NIHR WoundTec HTC The use of Moleculight in the management of diabetic foot ulcers: a pilot study; NIHR WoundTec HTC M23605), and Co-Applicant (VASGBI NIAA The role of preoperative assessment in effective vascular multidisciplinary team decision making (WKR0-2017-0032); and a randomised controlled trial of swab versus tissue sampling for infected diabetic foot ulcers, and comparison of culture versus molecular processing techniques (NIHR HTA 16/163/04)). All the aforementioned studies are unrelated to the scope of this review. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR, University of Leeds, NHS, or the UK Department of Health and Social Care.

HS: works as a Consultant Podiatrist at Leeds Teaching Hospitals NHS Trust.

SR: none known.

EM: has declared that her current post is funded indirectly through a research grant from the NIHR HTA programme for work on a randomised controlled trial of an intervention for surgical wound healing in skin cancer patients (NIHR151863). This work is unrelated to the current review. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR, University of Leeds, NHS, or the UK Department of Health and Social Care.

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Registration and protocol

Protocol (2021): 10.1002/14651858.CD013857

History

Protocol first published: Issue 1, 2021

Data, code and other materials

As part of the published Cochrane review, the following is made available for download for users of the Cochrane Library: Full search strategies for each database; full citations of each unique report for all studies included, ongoing or waiting classification, or excluded at the full text screen, in the final review; and consensus risk of bias assessments. Analyses and data management were conducted within Cochrane's authoring tool, RevMan, using the inbuilt computation methods (Supplementary material 7).

Notes

Parts of the methods section of this protocol are based on a standard template established by the Cochrane Vascular Group.

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INDEX TERMS

Medical Subject Headings (MeSH)

*Amputation, Surgical [adverse effects] [statistics & numerical data]; Lower Extremity [blood supply] [surgery]; Peripheral Arterial Disease [surgery]; *Randomized Controlled Trials as Topic

MeSH check words

Humans