Patient-centered Outcomes for Individuals with a Venous Leg Ulcer: A Scoping Review

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CME
1 AMA PRA Category 1 Credit™

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GENERAL PURPOSE: To summarize randomized clinical trials addressing patient-centered outcomes of individuals with a venous leg ulcer.
TARGET AUDIENCE: This continuing education activity is intended for physicians, physician assistants, nurse practitioners, and nurses with an interest in skin and wound care.
LEARNING OBJECTIVES/OUTCOMES: After participating in this educational activity, the participant will:
1. Summarize the results of the review of randomized controlled trials addressing patient-centered outcomes of individuals with a venous leg ulcer.
2. Identify the limitations of the research analyzed for the review.

ABSTRACT

OBJECTIVE: To summarize randomized clinical trials addressing patient-centered outcomes of individuals with a venous leg ulcer with a scoping review.
DATA SOURCES: Authors searched PubMed using MESH terms for "venous ulcer" AND "randomized" for randomized clinical trials published from January 2002 to October 2021 that explored content-validated patient-centered outcomes for individuals with a clinically diagnosed venous leg ulcer. Authors also searched Cochrane Reviews from inception to April 15, 2022 for additional references using the same MESH terms.
STUDY SELECTION: Studies in any setting were included if primary or secondary outcomes were venous ulcer-related mobility, pain or analgesic use, healing, infection, quality of life (including odor, social isolation, depression), amputation, or patient-level costs of treatment. Preclinical or nonrandomized clinical studies or those without venous leg ulcers were excluded.
DATA EXTRACTION: Authors tabulated interventions studied, numbers of patients treated per group, risk of delayed ulcer healing, and statistical significance of comparisons of 485 qualifying articles in Google Sheets.
DATA SYNTHESIS: Authors graphically represented and tabulated frequencies of studies addressing patient-centered outcomes of individuals with venous ulcers. Studies mainly reported effects of compression, dressings, topical antimicrobials, or systemic therapy on patient healing or pain outcomes. Related ischemia, ultrasonography, or risk factors for delayed healing were not consistently reported, inflating variability of outcomes and decreasing consistency of differences reported.
CONCLUSIONS: Research is needed on the mobility, amputation risk, infection risk, quality of life, and healthcare costs of patients with venous ulcers. Promising interventions include grafts, exercise, analgesics, electrical modalities, negative pressure, or vascular interventions. Consistently reporting each patient's baseline ischemia and vascular condition would improve relevance.
KEYWORDS: patient-centered, randomized clinical trials, scoping review, venous insufficiency, venous leg ulcer

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INTRODUCTION

Venous leg ulcers (VUs) are wounds of the lower leg that heal more slowly than expected because of insufficient flow of venous blood and lymphatic fluid from the lower leg toward the heart. They affect 3% to 5% of those older than 65 years in developed countries[1] and account for 1% to 4% of healthcare costs in reporting countries, equating to more than US $10 billion worldwide.[2] Actual costs may be higher because VUs are often underdiagnosed.[3] Historically, VU interventions have paralleled the course of medical progress (Table 1).[4–32] Randomized clinical trial (RCT) scrutiny of treatment efficacy and safety outcomes has increased during the past 4 decades. Although considerable non-RCT research has been devoted to describing the clinical and economic burdens of VU to institutions or countries,[2] RCTs supporting comparative efficacy of interventions aimed to improve patient-centered outcomes (PCOs) of individuals with VUs have rarely been reviewed. These recently content-validated PCOs include pain, delayed healing, wound infection, quality of life (ie, depression, odor, and social isolation), physical function/ambulation, and patient-related costs (eg, unreimbursed care or loss of employment).[33]

Objective

In this scoping literature review, the authors explored the extent to which RCTs measuring PCOs of VUs have reported effects on valid PCOs during the past 40 years.

METHODS

Two authors searched the National Institutes of Health National Library of Medicine PubMed electronic reference database from January 1, 2002, to October 31, 2021, for original VU RCTs reporting at least one PCO.

Table 1. HISTORIC VENOUS LEG ULCER (VU) MANAGEMENT IN THE CONTEXT OF MEDICAL HISTORY

VU-Based Discoveries	Year	General Medicine Discoveries
	~2500 BC	Honey first used on wounds[4]
Hippocrates writes about VUs and best treatment[5] practices	460–370 BC	
	1803	Morphine discovered[6]
	1867	First antiseptic[7]
	1869	First skin transplant[8]
	1882	Function of platelets discerned[9]
Unna boot invented[10]	1885	
	1915	Heparin discovered[11]
Antiseptics used to treat VU[12]	1926	
First article published listing injection near the site of the ulcer for obliteration of the veins[13]	1928	Penicillin discovered[14]
First article published with compression therapy[15]	1930	
Aspirin powder on the wound as analgesic[16]	1931	
First article published with ligation of the saphenous vein[17]	1940	
First article published with pinch graft being used on ulcer[18]	1943	
First article published listing blood product as treatment for VU[19]	1946	
First published use of trypsin as treatment for cutaneous ulcers[20]	1953	First working laser made[21]
	1956	Ultrasound information is compiled[22]
	1969	Hyperbaric oxygen therapy is used on wounds[23]
First trial published with ultrasound therapy[24]	1976	
	1981	First artificial skin is used[25]
First article published using lasers as treatment[26]	1982	
	1983	First successful clinical use of cultured human keratinocytes (the first successful culture was reported in 1979)[27]
First article published using a hydrocolloid dressing[28]	1985	
Four-layer bandage created[29]	1993	
First article published using hyaluronic acid as a treatment[30]	1996	
	2003	Completion of the Human Genome Project[31]
First article published using biocellulose[32]	2012	

Table 2. SYNONYMS INCLUDED FOR PATIENT-CENTERED VENOUS LEG ULCER (VU) OUTCOMES

Patient-Centered Outcome	Included Synonyms
Improved physical function	Increased walking or performance of daily activities
Decreased VU pain	Decreased analgesic use
Improved VU healing rate	Shorter healing time, increased percent reduction in VU area, or greater percentage of study participants healed during a time period that was established before the study
Lower amputation risk	Reduced incidence of major or minor amputations during a prestudy established time frame
Improved VU-related quality of life	Quality of life measures validated for patients with VUs, including reduced VU odor, social isolation, and depression
Reduced patient costs	Lower costs to patient, reduced economic burden (eg, reduced income loss because of less need for VU home care)
Lower VU infection rates	Reduced incidence of standardized wound infection measures, signs, or symptoms

The MESH terms searched were: "randomized, clinical trial OR review," combined with the MESH terms for "venous leg ulcer." Original studies were included if they reported at least one effect on a PCO content-validated as a relevant wound outcome or endpoint for wound care patients by multidisciplinary respondents to a standardized online survey,[33] as listed in Table 2. Studies were excluded if they were not randomized (because of the potential for bias in patient assignment to treatment), if they duplicated data reported in another included study, or if no effect was reported on a patient with a clinically diagnosed VU.

Results were tabulated and shared in Google Sheets listing the following data for each RCT: first author, year of publication, interventions, numbers of participants per group, and $P < .05$ representing statistical significance. Risk of VU nonhealing within 24 weeks[34] was also included as (1) low: <5-cm^2 VU area and < 6 months' duration; (2) moderate, mixed, or unknown: 5- to 10-cm^2 area and 6 to 12 months' duration; or (3) high: >10-cm^2 area and >12 months' duration. Entries were checked for accuracy by a third author.

All results were checked for validity against evidence retrieved from Cochrane Reviews identified in an updated PubMed search of combined MESH terms for VU and Cochrane Review from inception to April 15, 2022. Additional original RCTs derived from these Cochrane Reviews were included in the Google Sheets file coded as derivative references, extending the time for included RCTs to the past 40 years.

Frequencies of tabulated RCTs exploring each of the PCO categories for patients with a VU at reported levels of risk of delayed healing were planned for graphic display. However, because VU risk of delayed healing was so rarely controlled or reported, the authors instead graphed frequencies of RCTs without indicating enrolled patients' risk of delayed VU healing.

Interventions used in the RCTs were categorized with the goal of tabulating research density and consistency for the effects of each major category of intervention on each PCO (Table 3). Research density for each combination of intervention category and PCO was defined as the total number of qualifying RCTs identified that compared the effects of one or more interventions in the category on the indicated PCO. Consistency of evidence was defined as the number of comparisons reaching statistical significance ($P < .05$) when an intervention in that category was compared with any other intervention within a qualifying RCT to test for the effects on the indicated PCO. This was done to assess the capacity of that PCO measure to reflect the consistent effects of interventions, not to support efficacy of any specific intervention in the category.

RESULTS

A total of 1,006 articles were returned by the original literature search, and 197 were returned by the confirming search of related Cochrane Reviews. In all, 485 original unique RCTs on a total of 46,504 patients qualified for inclusion in the analysis, including 31 RCTs derived from systematic Cochrane Reviews (Figure 1).[35]

To answer the question, "Which PCOs have been studied in RCTs enrolling patients with a VU?" the authors tabulated frequencies of reporting a comparative effect of two or more treatments on each PCO measured (Figure 2). Many RCTs compared more than two interventions on more than one PCO. As a result, among the 485 RCTs summarized, there were 697 comparisons of treatment effects on one or more PCOs for patients with a VU. Among these comparisons, statistically significant ($P < .05$) comparative PCO improvements were reported in response to at least one study treatment in 261 (37.4%) of the intervention comparisons.

The most common PCOs studied were improved VU healing, reported in 465 (95.8%) of the RCTs, and decreased pain, reported in 71 (14.6%) of the RCTs (Figure 2). Improved quality of life, patient costs, and infection rates were each reported in less than 10% of RCTs. Improved mobility/walking or lower amputation risk were reported in less than 1% of the RCTs identified.

Table 3. CONSISTENCY/DENSITY RATIOS FOR RANDOMIZED CLINICAL TRIALS (RCTs) MEASURING PATIENT-CENTERED OUTCOMES (PCOs) FOR PATIENTS WITH VENOUS LEG ULCERS RECEIVING DIFFERENT CATEGORIES OF INTERVENTIONS

Intervention	Mobility/ Total Mobility	Pain/ Total Pain	Healing/ Total Healing	Amputations/ Total Amputations	QoL/ Total QoL	Patient Costs/ Total Patient Costs	Infection/ Total Infection	All PCOs/ Total RCTs	Most Common PCOs
Exercise (physical therapy, leg clubs, home visits, coaching)	0/2	2/3	7/14		3/4	1/3		13/26	Healing, QoL
Cleanser (water, saline, surfactant)		0/1	1/3					1/4	Healing
Compression (short-stretch multilayer, one-layer, intermittent)		6/16	36/88		6/16	4/13	0/2	54/125	Healing, QoL, pain, patient costs
Debriding agents (dextranomer, enzyme, larval)		1/2	7/14		0/2	0/2	1/1	9/21	Healing, patient costs, infection
Dressings (film, foam, hydrocolloid, gauze)		2/9	15/80		0/2	1/10	0/7	18/108	Healing, patient costs, infection
Analgesic (topical lidocaine 2.5%, prilocaine 2.5% cream, systemic ibuprofen, aspirin)		8/8	1/10					9/18	Healing, pain
Antimicrobial (silver, iodine, hydrogen peroxide, sulfhydryl, octenidine, merbromin)		6/9	18/56		0/4	1/4	2/9	27/82	Healing, pain, infection, patient costs
Electrical/electromagnetic field (direct/alternating current, pulsed electromagnetic field)	1/1	5/9	13/20		0/2			19/32	Healing, pain
Growth factors—topical (platelet-derived growth factor, platelet-rich plasma)		1/2	6/26		0/1		2/2	9/31	Healing, pain, infection
Humectant (hydrogel, honey, hyaluronic acid derivatives)		1/4	10/24		0/1	2/3	0/1	13/33	Healing, pain, patient costs
Negative-pressure therapy		1/1	3/3		1/1	1/2	2/2	8/9	Healing, pain, QoL, infection
Physical (heat, ultrasound, laser, shockwave)		3/4	15/35		0/2		1/2	19/43	Healing, pain, infection
Systemic therapy (flavonoids, vasoactive agents, hyperbaric oxygen, pentoxifylline)		2/6	28/81	1/1	1/2	1/4		33/94	Healing, amputation, QoL, patient costs, infection
Vascular (endovenous ablation, vein surgery, sclerotherapy)		1/2	9/18		1/3		2/2	13/25	Healing, infection, QoL
Grafts (allografts, autografts, artificial skins, sprayed cells)			18/34			0/1	0/1	18/36	Healing
Totals	1/3	39/76	187/506	1/1	12/40	11/42	10/29	261/697	

Note: QoL, quality of life. Intervention examples are local unless otherwise stated. Data shown are consistency, defined as the number of RCTs reporting significant effects ($P < .05$) within each broad intervention category/research density, or the total number of comparisons measuring the indicated PCO in RCTs comparing at least one agent in that category of intervention. Higher ratios of significant effects/total RCTs suggest a trend toward more consistently reported effects of agents in that intervention category on the indicated PCO. Lower or absent ratios suggest opportunities for further research.

Patient risk of nonhealing was inconsistently controlled or reported. Among the 485 qualifying RCTs, 450 (71%) of RCTs enrolled patients with VU of mixed or unknown risk of delayed healing, defined as nonhealing within 24 weeks. Among the 465 RCTs reporting healing, 26 (5.6%) enrolled only patients at low risk of delayed healing, and 109 (23.4%) enrolled only patients at high risk of delayed healing. In the 71 RCTs reporting VU-related pain, 26 (36.6%) enrolled only patients at low risk, and 18 (25.3%) enrolled only patients at high risk of delayed healing.

Of the 697 intervention comparisons made in these 485 RCTs, 144 (22.9%) PCO comparisons were made on

patients with high risk of nonhealing and 36 (5.7%) on those at low risk of nonhealing. The remainder of studies and comparisons did not report or adjust for VU risk of nonhealing within 24 weeks.

Interventions most frequently studied (Table 3) were compression modalities, dressings, topical antimicrobial agents, and systemic or physical therapies. Significant ($P < .05$) comparative PCO benefits were reported for healing, pain, quality of life, or patient cost outcomes in up to half of RCTs comparing one or more compression and antimicrobial, systemic, or physical therapy modalities. Important research gaps were noted for the PCOs of VU-related infection and patient costs, with approximately 1 in 3 comparisons reporting an effective ($P < .05$) benefit for these PCOs.

Significantly improved mobility and amputation prevention were reported in only one small RCT each. In one RCT comparing two levels of electromagnetic therapy with conventional dressings, all 19 participants in the three groups improved in mobility during the 50-day study ($P < .05$).[36] In the second study, adding six 90-minute sessions per week of hyperbaric oxygen therapy at 2.5 ATA to conventional therapy across a total of 30 days increased local tissue partial pressure of oxygen ($P < .05$).[37] In addition, this treatment reduced the likelihood of amputations in 15 patients with a chronic, nonhealing ulcer who were at high risk of delayed healing, compared with 15 similar patients receiving conventional therapy only.[37]

As with many RCTs identified in this work, accurate differential diagnosis of VU etiology was not definitively confirmed by either ankle-brachial index (the ratio of affected ankle systolic BP divided by the corresponding brachial systolic BP) or duplex ultrasonography, which maps the anatomy of venous insufficiency.[38]

Table 3 displays the relative density (number of intervention comparisons) and consistency (number of reported significant differences between intervention effects on each PCO) using each major category of intervention. Higher density indicates areas of research with more studies exploring the effects of that intervention category on the indicated PCO. Lower ratios of consistent effects suggest opportunities for research to confirm or reject clinical efficacy of interventions in that category. Higher consistency suggests that at least one intervention in the category was reported to significantly improve the indicated PCO for VUs, a potential area for clinical practice opportunities.

Most studies in each intervention category explored healing and/or pain PCOs (Table 3). Compression and

Figure 1. LITERATURE SEARCH STRUCTURE AND DISPOSITION OF RECORDS

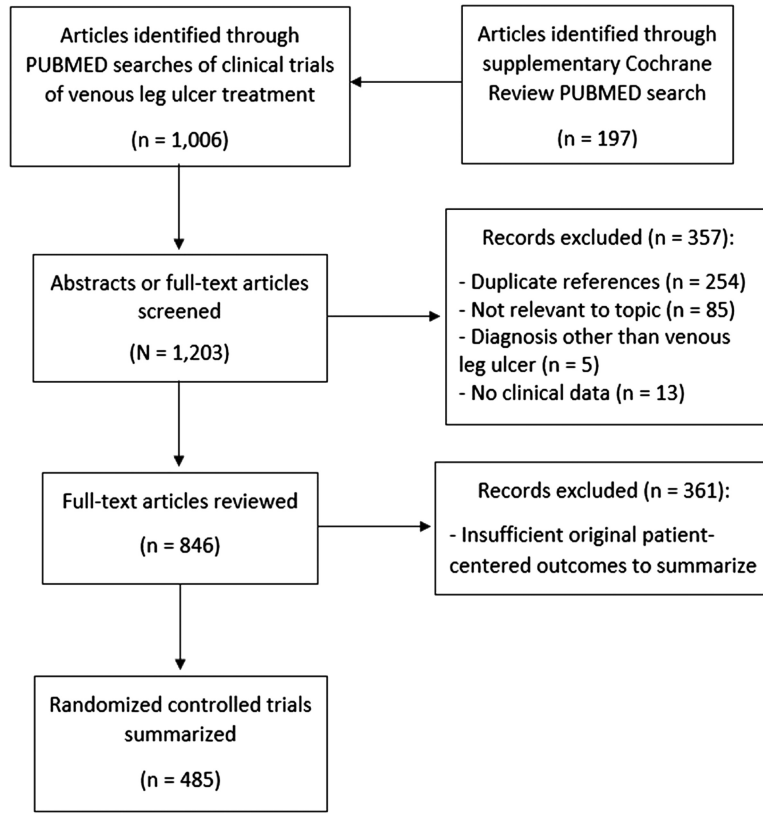
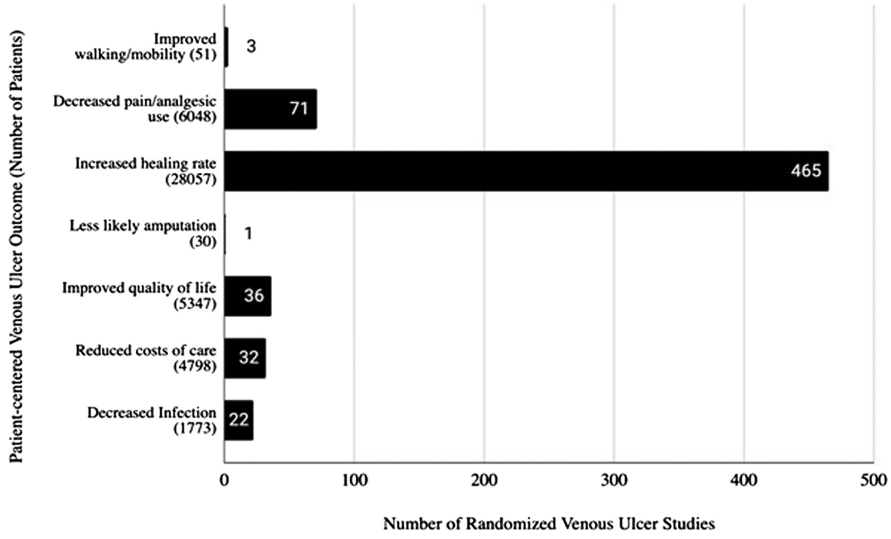


Figure 2. NUMBERS OF VENOUS LEG ULCER STUDIES REPORTING EACH VALID PATIENT-CENTERED OUTCOME SINCE 1970



wound dressing interventions were compared in the most qualifying RCTs, followed by systemic vascular therapies such as pentoxifylline, herbal agents, or flavonoids. Statistically significant findings generally paralleled density trends. The most consistent effects were reported for exercise, electrical or electromagnetic field stimulation, negative-pressure therapy, and vascular or grafting interventions.

DISCUSSION

A disproportionately high number of RCTs on patients with a VU documented comparative healing efficacy of different interventions. This suggests that research has focused on VU healing rather than other PCOs important to patients. Whatever regulatory or other issues have caused this trend, it has disserved patient interests, leaving important research gaps testing safety and efficacy of interventions aimed to improve patient mobility, amputation or infection incidence or severity, patient-related costs, quality of life, and pain outcomes. Increased walking contributes to a variety of health benefits[39] and is associated with faster VU healing,[40] illustrating the critical role of ambulation in VU recovery, yet it was rarely measured as an outcome.

The finding of statistically significant differences for each PCO suggests that current PCO measures are sufficiently consistent and reliable to generate meaningful comparative intervention effects. It should be noted that some PCOs are not independent of others. For example, pain substantially affects a patient's quality of life and patient-related costs. Future research may address these interacting outcome measures to clarify PCOs for patients with a VU.

Many RCTs analyzed described VU without performing a definitive diagnosis assessing the pedal pulse and, if absent, using an ankle-brachial index to determine the extent of lower limb ischemia in the leg with a suspected VU. Identifying coetiologies such as ischemia or neuropathy is vitally important in determining the course of patient care, yet neither etiology was consistently reported in the RCTs found in this literature review. Few RCTs used duplex ultrasonography to map the venous insufficiency location(s). These practices are especially important for VUs that do not decrease in area by at least 40% after 3 weeks of treatment, because this indicates that they are unlikely to heal in 12 weeks.[41] These findings suggest the need for consistently improved clinical practice to include diagnostic tools to assess ischemia and neuropathy to inform effective VU management decisions supporting PCOs. Research exploring the efficacy and safety of VU interventions would provide a better evidence foundation if it reported PCOs controlling or adjusting for levels of ischemia, neuropathy, and sites of venous insufficiency.

Most qualifying RCTs did not control participants' risk of delayed healing. This practice increased variability of clinical healing rates, inflating error variance, which reduced the likelihood of statistically significant differences between healing effects of interventions studied. Future VU research would be more fruitful if it uniformly reported, controlled, and/or adjusted analyses for patient risk of delayed healing.

Table 1 illustrates how VU treatments expanded to include new medical discoveries. As an example, clinical practice improved following compression-related discoveries. Ensuing RCTs lead to guideline recommendations for patient-appropriate use of effective sustained, multilayer compression.[42–44]

Table 1 also shows how wound care professionals were willing to try a wide variety of treatments hoping one might work on their patients with VUs. If this pattern continues, there may follow a surge of research in gene therapy for patients with a VU of genetic etiology.

Table 3 summarizes the PCO RCT findings to explore consistency of findings within major categories of interventions. Systemic treatments studied in qualifying RCTs included a wide variety of antimicrobial, anti-inflammatory, antihypertensive, or immunomodulating agents, including one agent prescribed for stomach ulcers and another for seizures.

Although no single intervention or category of interventions supported improvements in all PCOs reviewed in this study, RCT research supported improved healing or pain in patients with a VU managed with multilayer, patient-appropriate compression; pentoxifylline as a systemic therapy; endovenous as opposed to open surgery; and cadexomer iodine as a topical antimicrobial agent. The efficacy of any individual intervention was not systematically reviewed, because the goal of this review was to focus on which PCOs were addressed in the field. Those seeking current evidence-based bundles of interventions to optimize VU PCOs will find details and references supporting effective compression, elevation, exercise, vascular, and other interventions in recent multidisciplinary guidelines for managing those with a VU.[42–44]

Opportunities for RCT research to clarify intervention efficacy were suggested by consistent research in this review, indicated by at least half of RCTs in an intervention category with $P < .05$. These include coached exercise (13 of 26 RCTs), electrical modalities (19 of 32 RCTs), vascular interventions (13 of 25 RCTs), and cutaneous grafts (18 of 36 RCTs). Hyperbaric oxygen, used as an adjunctive intervention in three RCTs,[37,45,46] significantly improved healing, but only one of these studies identified the ulcers as being of venous etiology. These findings merit replication on VUs with clearly identified levels of ischemia and locations of vascular insufficiency.

A limitation of this research is that in many of the summarized RCTs, VUs had unidentified levels of ischemia, neuropathy, or site(s) of venous insufficiency. In conducting this review, the authors set out to determine how well research was meeting patient needs. The unexpected discovery was that most VU research was conducted without the benefit of accurate baseline diagnoses of the extent of ischemia or vascular pathology contributing to the patient's VU chronicity. This information is fundamental for supporting effective clinical practice decisions. It empowers clinicians to cure the patient instead of only caring for the wound. Research on VUs would better inform clinical practice and improve patient outcomes by consistently reporting and analyzing results as related to valid measures of each patient's baseline VU ischemia and vascular pathology.

CONCLUSIONS

The RCT literature on VUs is rich with studies reporting healing and pain, key PCOs. However, the predominance of wound healing and pain outcomes reported in RCTs studying patients with a VU suggests a research focus on the VU itself, rather than on what matters to patients. More RCT research is needed exploring intervention effects on increased mobility, quality of life, reduced patient costs, and likelihood of amputation or infection, all of which are PCOs important to patients' recovery, economic survival, social independence, and well-being. Clarity of PCO results and VU clinical practice decisions would improve with more consistent VU RCT reporting and risk-adjusted analyses of patient risk factors for delayed healing, including measures of ischemia and ultrasonographic mapping of vascular insufficiency.

PRACTICE PEARLS

- Measuring PCOs informs wound care professionals about how well they are meeting their patients' needs.
- Among the 485 RCTs identified in this scoping review, the most frequently measured PCOs were healing or pain.
- Important opportunities exist for RCT research to address patient needs, including to improve walking or mobility, improve quality of life, reduce out-of-pocket costs, and reduce amputation or infection likelihood.
- At least half of the RCTs yielded statistically significant results of interventions for patients with VUs, highlighting potential opportunities for research and practice. These include exercise, compression, analgesics, grafts, electrical/electromagnetic stimulation, negative-pressure therapy, or vascular interventions. ●

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