Journal of Vascular Surgery®

February 2016
Volume 63, Issue 2, Supplement, p1S-68S

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The Management of Diabetic Foot: A Clinical Practice Guideline by the Society for Vascular Surgery in Collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine

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A systematic review and meta-analysis of off-loading methods for diabetic foot ulcers

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INTRODUCTION

Ulceration of the foot in diabetes is a common complication, can be disabling, and frequently leads to amputation of the leg. The lifetime risk for foot ulcers in people with diabetes has been estimated to be 15% to 25%. Diabetic foot ulcers (DFUs) are associated with adverse sequelae, high costs, and decreased quality of life. The patients with DFU often are found to have depression after the diagnosis of DFU and have high rates of associated mortality. This increases the burden on the patient, the patient's family, and society. Whereas worldwide data are not available, ulcer care adds around US$9 billion to $13 billion to the direct yearly costs associated with diabetes itself.

The combination of advanced peripheral arterial disease, infection, and neuropathy that often results in DFU makes DFU even more difficult to treat successfully. Even after they have healed, DFUs still have high rates of recurrence. The complexity of the various disease processes that cause these ulcers often requires a multidisciplinary approach. As such, representatives from the Society for Vascular Surgery, the American Podiatric Medical Association, and the Society for Vascular Medicine worked together to review the literature and to develop recommendations on the management of the DFU. In this supplement, we summarize and appraise the best available evidence for the diagnosis and treatment of the DFU and present recommendations for practicing clinicians.

THE GUIDELINE DOCUMENT

The Society for Vascular Surgery Diabetic Foot Ulcer Guidelines Committee identified five key areas of focus for DFU (prevention, diagnosis of osteomyelitis, wound care, off-loading, and peripheral arterial disease). Each group of the committee was assigned a focus area. Within each section, the key clinical questions and relevant evidence are summarized. The guideline committee incorporated the evidence with their clinical expertise and considered patients' values and preferences following the GRADE approach (Grades of Recommendation Assessment, Development, and Evaluation).

Strong recommendations imply high confidence that patients will be better off following the recommended action and that minimal variation in care is expected. Conversely, weak (also called conditional) recommendations imply that benefits and risks are more closely matched and are more dependent on specific clinical scenarios. Therefore, the recommended action is appropriate for only some patients, and alternative actions may be considered.

COMMISSIONED SYSTEMATIC REVIEWS

The committee deemed five key questions to be in need of a full systematic review and meta-analysis; the evidence in several other areas was summarized by consensus of committee members. The five systematic reviews addressed the effect of glycemic control on preventing DFU, the evidence supporting different off-loading methods, adjunctive therapies, débridement, and tests to predict wound healing. Numerous randomized controlled trials were identified in every systematic review; however, most of these trials were small. Therefore, searches were expanded to include nonrandomized trials as well.

IMPLEMENTATION

We encourage dissemination and implementation of this clinical practice guideline through multiple strategies. Dissemination to vascular surgeon trainees can be performed through incorporating the evidence in didactics, in-training examinations, and specialty board reviews. Developing algorithms for the management of DFU based on this guideline can be incorporated in electronic medical records to remind practicing clinicians what treatment to offer and when. Unfortunately, it is common to see in practice DFU patients in whom off-loading is not properly prescribed or performed or in whom certain approaches are not discussed and omitted. Therefore, such algorithms will lead to a certain level of standard approach beyond which individualizing therapy can be undertaken. Last, shared decision-making tools (ie, decision aids) are needed to guide patients and clinicians when important decisions are entertained and tradeoffs are being considered. Hardly any of these exist to support decision-making in DFU.

FUTURE DIRECTIONS

This endeavor led by the Society for Vascular Surgery highlighted the need for more high-quality research on DFU. We anticipate that identifying patients for future research is not difficult because DFU is common. The challenge lies in producing unbiased estimates. We observed in the literature clear signs of confounding by indication, selection bias, and unblinded assessment of outcomes (eg, wound size). The randomized controlled study design with blinding of outcome assessors is highly recommended for future studies. The outcome of wound size should be replaced by complete wound healing, a more objective outcome that is more important to patients. Stratification by clinical prognostic factors such as anatomic wound location, vascular status, and other comorbidities is also important to yield practical findings

Author conflict of interest: none.
J Vasc Surg 2016;63:1S-2S
0741-5214

http://dx.doi.org/10.1016/j.jvs.2015.10.085

more helpful for patients and surgeons. Last, the current literature is fraught with comparisons of active interventions to standard therapy. Such standard therapy is usually poorly described and heterogeneous and should be explicitly reported in the future.

The dynamic nature of research and evolving evidence necessitates updating this guideline. We anticipate to revisit this topic in 5 years and sooner if emerging evidence becomes available. We hope that specialists treating DFU and referring clinicians alike will find value in the effort put forth in this supplement and that this will ultimately lead to improved quality of patient care.

Anil Hingorani, MD

The management of diabetic foot: A clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine

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Background: **Diabetes mellitus continues to grow in global prevalence and to consume an increasing amount of health care resources. One of the key areas of morbidity associated with diabetes is the diabetic foot. To improve the care of patients with diabetic foot and to provide an evidence-based multidisciplinary management approach, the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine developed this clinical practice guideline.**

Methods: **The committee made specific practice recommendations using the Grades of Recommendation Assessment, Development, and Evaluation system. This was based on five systematic reviews of the literature. Specific areas of focus included (1) prevention of diabetic foot ulceration, (2) off-loading, (3) diagnosis of osteomyelitis, (4) wound care, and (5) peripheral arterial disease.**

Results: **Although we identified only limited high-quality evidence for many of the critical questions, we used the best available evidence and considered the patients' values and preferences and the clinical context to develop these guidelines. We include preventive recommendations such as those for adequate glycemic control, periodic foot inspection, and patient and family education. We recommend using custom therapeutic footwear in high-risk diabetic patients, including those with significant neuropathy, foot deformities, or previous amputation. In patients with plantar diabetic foot ulcer (DFU), we recommend off-loading with a total contact cast or irremovable fixed ankle walking boot. In patients with a new DFU, we recommend probe to bone test and plain films to be followed by magnetic resonance imaging if a soft tissue abscess or osteomyelitis is suspected. We provide recommendations on comprehensive wound care and various débridement methods. For DFUs that fail to improve (>50% wound area reduction) after a minimum of 4 weeks of standard wound therapy, we recommend adjunctive wound therapy options. In patients with DFU who have peripheral arterial disease, we recommend revascularization by either surgical bypass or endovascular therapy.**

Conclusions: **Whereas these guidelines have addressed five key areas in the care of DFUs, they do not cover all the aspects of this complex condition. Going forward as future evidence accumulates, we plan to update our recommendations accordingly. (J Vasc Surg 2016;63:3S-21S.)**

Diabetes is one of the leading causes of chronic disease and limb loss worldwide, currently affecting 382 million people. It is predicted that by 2035, the number of reported diabetes cases will soar to 592 million.[1] This disease affects the developing countries disproportionately as >80% of diabetes deaths occur in low- and middle-income countries.[2]

As the number of people with diabetes is increasing globally, its consequences are worsening. The World

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Author conflict of interest: none.

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0741-5214

http://dx.doi.org/10.1016/j.jvs.2015.10.003

SUMMARY OF RECOMMENDATIONS

1. Prevention of diabetic foot ulceration

Recommendation 1: We recommend that patients with diabetes undergo annual interval foot inspections by physicians (MD, DO, DPM) or advanced practice providers with training in foot care (Grade 1C).
Recommendation 2: We recommend that foot examination include testing for peripheral neuropathy using the Semmes-Weinstein test (Grade 1B).
Recommendation 3: We recommend education of the patients and their families about preventive foot care (Grade 1C).
Recommendation 4:
a. We suggest against the routine use of specialized therapeutic footwear in average-risk diabetic patients (Grade 2C).
b. We recommend using custom therapeutic footwear in high-risk diabetic patients, including those with significant neuropathy, foot deformities, or previous amputation (Grade 1B).
Recommendation 5: We suggest adequate glycemic control (hemoglobin $A_{1c} < 7\%$ with strategies to minimize hypoglycemia) to reduce the incidence of diabetic foot ulcers (DFUs) and infections, with subsequent risk of amputation (Grade 2B).
Recommendation 6: We recommend against prophylactic arterial revascularization to prevent DFU (Grade 1C).

2. Off-loading DFUs

Recommendation 1: In patients with plantar DFU, we recommend offloading with a total contact cast (TCC) or irremovable fixed ankle walking boot (Grade 1B).
Recommendation 2: In patients with DFU requiring frequent dressing changes, we suggest off-loading using a removable cast walker as an alternative to TCC and irremovable fixed ankle walking boot (Grade 2C). We suggest against using postoperative shoes or standard or customary footwear for off-loading plantar DFUs (Grade 2C).
Recommendation 3: In patients with nonplantar wounds, we recommend using any modality that relieves pressure at the site of the ulcer, such as a surgical sandal or heel relief shoe (Grade 1C).
Recommendation 4: In high-risk patients with healed DFU (including those with a prior history of DFU, partial foot amputation, or Charcot foot), we recommend wearing specific therapeutic footwear with pressure-relieving insoles to aid in prevention of new or recurrent foot ulcers (Grade 1C).

3. Diagnosis of diabetic foot osteomyelitis (DFO)

Recommendation 1: In patients with a diabetic foot infection (DFI) with an open wound, we suggest doing a probe to bone (PTB) test to aid in diagnosis (Grade 2C).
Recommendation 2: In all patients presenting with a new DFI, we suggest that serial plain radiographs of the affected foot be obtained to identify bone abnormalities (deformity, destruction) as well as soft tissue gas and radiopaque foreign bodies (Grade 2C).
Recommendation 3: For those patients who require additional (ie, more sensitive or specific) imaging, particularly when soft tissue abscess is suspected or the diagnosis of osteomyelitis remains uncertain, we recommend using magnetic resonance imaging (MRI) as the study of choice. MRI is a valuable tool for diagnosis of osteomyelitis if the PTB test is inconclusive of if the plain film is not useful (Grade 1B).
Recommendation 4: In patients with suspected DFO for whom MRI is contraindicated or unavailable, we suggest a leukocyte or antigranulocyte scan, preferably combined with a bone scan as the best alternative (Grade 2B).
Recommendation 5: In patients at high risk for DFO, we recommend that the diagnosis is most definitively established by the combined findings on bone culture and histology (Grade 1C). When bone is débrided to treat osteomyelitis, we recommend sending a sample for culture and histology (Grade 1C).
Recommendation 6: For patients *not* undergoing bone débridement, we suggest that clinicians consider obtaining a diagnostic bone biopsy when faced with diagnostic uncertainty, inadequate culture information, or failure of response to empirical treatment (Grade 2C).

4. Wound care for DFUs

Recommendation 1: We recommend frequent evaluation at 1- to 4-week intervals with measurements of diabetic foot wounds to monitor reduction of wound size and healing progress (Grade 1C).

Recommendation 1.1: We recommend evaluation for infection on initial presentation of all diabetic foot wounds, with initial sharp débridement of all infected diabetic ulcers, and urgent surgical intervention for foot infections involving abscess, gas, or necrotizing fasciitis (Grade 1B).

Recommendation 1.2: We suggest that treatment of DFIs should follow the most current guidelines published by the Infectious Diseases Society of America (IDSA) (Ungraded).

Recommendation 2: We recommend use of dressing products that maintain a moist wound bed, control exudate, and avoid maceration of surrounding intact skin for diabetic foot wounds (Grade 1B).

Recommendation 3: We recommend sharp débridement of all devitalized tissue and surrounding callus material from diabetic foot ulcerations at 1- to 4-week intervals (Grade 1B).

Recommendation 4: Considering lack of evidence for superiority of any given débridement technique, we suggest initial sharp débridement with subsequent choice of débridement method based on clinical context, availability of expertise and supplies, patient tolerance and preference, and cost-effectiveness (Grade 2C).

Recommendation 5: For DFUs that fail to demonstrate improvement (>50% wound area reduction) after a minimum of 4 weeks of standard wound therapy, we recommend adjunctive wound therapy options. These include negative pressure therapy, biologics (platelet-derived growth factor [PDGF], living cellular therapy, extracellular matrix products, amnionic membrane products), and hyperbaric oxygen therapy. Choice of adjuvant therapy is based on clinical findings, availability of therapy, and cost-effectiveness; there is no recommendation on ordering of therapy choice. Re-evaluation of vascular status, infection control, and off-loading is recommended to ensure optimization before initiation of adjunctive wound therapy (Grade 1B).

Recommendation 6: We suggest the use of negative pressure wound therapy for chronic diabetic foot wounds that do not demonstrate expected healing progression with standard or advanced wound dressings after 4 to 8 weeks of therapy (Grade 2B).

Recommendation 7: We suggest consideration of the use of PDGF (becaplermin) for the treatment of DFUs that are recalcitrant to standard therapy (Grade 2B).

Recommendation 8: We suggest consideration of living cellular therapy using a bilayered keratinocyte/fibroblast construct or a fibroblast-seeded matrix for treatment of DFUs when recalcitrant to standard therapy (Grade 2B).

Recommendation 9: We suggest consideration of the use of extracellular matrix products employing acellular human dermis or porcine small intestinal submucosal tissue as an adjunctive therapy for DFUs when recalcitrant to standard therapy (Grade 2C).

Recommendation 10: In patients with DFU who have adequate perfusion that fails to respond to 4 to 6 weeks of conservative management, we suggest hyperbaric oxygen therapy (Grade 2B).

5. Peripheral arterial disease (PAD) and the DFU

Recommendation 1.1: We suggest that patients with diabetes have ankle-brachial index (ABI) measurements performed when they reach 50 years of age (Grade 2C).

Recommendation 1.2: We suggest that patients with diabetes who have a prior history of DFU, prior abnormal vascular examination, prior intervention for peripheral vascular disease, or known atherosclerotic cardiovascular disease (eg, coronary, cerebral, or renal) have an annual vascular examination of the lower extremities and feet including ABI and toe pressures (Grade 2C).

Recommendation 2: We recommend that patients with DFU have pedal perfusion assessed by ABI, ankle and pedal Doppler arterial waveforms, and either toe systolic pressure or transcutaneous oxygen pressure ($TcPO_2$) annually (Grade 1B).

Recommendation 3: In patients with DFU who have PAD, we recommend revascularization by either surgical bypass or endovascular therapy (Grade 1B).

Recommendation 3 (technical and implementation remarks)

- Prediction of patients most likely to require and to benefit from revascularization can be based on the Society for Vascular Surgery (SVS) Wound, Ischemia, and foot Infection (WIfI) lower extremity threatened limb classification.
- A combination of clinical judgment and careful interpretation of objective assessments of perfusion along with consideration of the wound and infection extent is required to select patients appropriately for revascularization.
- In functional patients with long-segment occlusive disease and a good autologous conduit, bypass is likely to be preferable.
- In the setting of tissue loss and diabetes, prosthetic bypass is inferior to bypass with vein conduit.
- The choice of intervention depends on the degree of ischemia, the extent of arterial disease, the extent of the wound, the presence or absence of infection, and the available expertise.

Health Organization projects that diabetes will be the seventh leading cause of death in 2030.[3] A further effect of the explosive growth in diabetes worldwide is that it has become one of the leading causes of limb loss. Every year, >1 million people with diabetes suffer limb loss as a result of diabetes. This means that every 20 seconds, an amputation occurs in the world as an outcome of this debilitating disease.[4] Diabetic foot disease is common, and its incidence will only increase as the population ages and the obesity epidemic continues.

Approximately 80% of diabetes-related lower extremity amputations are preceded by a foot ulcer. The patient demographics related to diabetic foot ulceration are typical for patients with long-standing diabetes. Risk factors for ulceration include neuropathy, PAD, foot deformity, limited ankle range of motion, high plantar foot pressures, minor trauma, previous ulceration or amputation, and visual impairment.[5] Once an ulcer has developed, infection and PAD are the major factors contributing to subsequent amputation.[6,7]

Available U.S. data suggest that the incidence of amputation in persons with diabetes has recently decreased; toe, foot, and below-knee amputation declined from 3.2, 1.1, and 2.1 per 1000 diabetics, respectively, in 1993 to 1.8, 0.5, and 0.9 per 1000 in 2009.[8] However, including the costs of outpatient ulcer care, the annual cost of diabetic foot disease in the United States has been estimated to be at least $6 billion.[9] A Markov modeling approach suggests that a combination of intensive glycemic control and optimal foot care is cost-effective and may even be cost-saving.[10]

DFUs and their consequences represent a major personal tragedy for the person experiencing the ulcer and his or her family[11] as well as a considerable financial burden on the health care system and society.[12] At least one-quarter of these ulcers will not heal, and up to 28% may result in some form of amputation. Therefore, establishing diabetic foot care guidelines is crucial to ensure the most cost-effective health care expenditure. These guidelines need to be goal focused and properly implemented.[13,14]

This progression from foot ulcer to amputation lends to several possible steps where intervention based on evidence-based guidelines may prevent major amputation. Considering the disease burden and the existing variations in care that make decision-making very challenging for patients and clinicians, the SVS, American Podiatric Medical Association, and Society for Vascular Medicine deemed the management of DFU a priority topic for clinical practice guideline development. These recommendations are meant to pertain to all diabetics regardless of etiology.

METHODS

The SVS, American Podiatric Medical Association, and Society for Vascular Medicine selected a multidisciplinary committee consisting of vascular surgeons, podiatrists, and physicians with expertise in vascular and internal medicine. A guideline methodologist, a librarian, and a team of investigators with expertise in conducting systematic reviews and meta-analysis assisted the committee in the process. The committee communicated in person and remotely repeatedly during a period of 3 years.

Specific questions were grouped into five areas of focus (prevention, diagnosis of osteomyelitis, wound care, offloading, and PAD). Each group of the committee was assigned a focus area. The committee deemed five key questions to be in need of a full systematic review and meta-analysis; the evidence in several other areas was summarized by consensus of committee members. The five systematic reviews addressed the effect of glycemic control on preventing DFU, the evidence supporting different off-loading methods, adjunctive therapies, débridement, and tests to predict wound healing.

The committee used the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) system[15] to rate the quality of evidence (confidence in the estimates) and to grade the strength of recommendations. This system, adopted by >70 other organizations, categorizes recommendations as *strong* Grade 1 or *weak* Grade 2 on the basis of the quality of evidence, the balance between desirable effects and undesirable ones, the values and preferences, and the resources and costs.

Grade 1 recommendations are meant to identify practices for which benefit clearly outweighs risk. These recommendations can be made by clinicians and accepted by patients with a high degree of confidence. Grade 2 recommendations are made when the benefits and risks are more closely matched and are more dependent on specific clinical scenarios. In general, physician and patient preferences play a more important role in the decision-making process in these circumstances.

In GRADE, the level of evidence to support the recommendation is divided into three categories: A (high quality), B (moderate quality), and C (low quality). Conclusions based on high-quality evidence are unlikely to change with further investigation, whereas those based on moderate-quality evidence are more likely to be affected by further scrutiny. Those based on low-quality evidence are the least supported by current data and the most likely to be subject to change in the future.

It is important to recognize that a Grade 1 recommendation can be based on low-quality (C) evidence by the effect on patient outcome. A full explanation of the GRADE system has been presented to the vascular surgery community.[15,16] A consensus of the recommendations and level of evidence to support it was attained, and every recommendation in this guideline represents the unanimous opinion of the task force. Although some recommendations are Grade 2 with Level 3 data, the task force deemed it appropriate to present these as the unanimous opinion of its members regarding optimal current management. This was done with the understanding that these recommendations could change in the future but that it was unlikely that new data would emerge soon. These guidelines are likely to be a "living

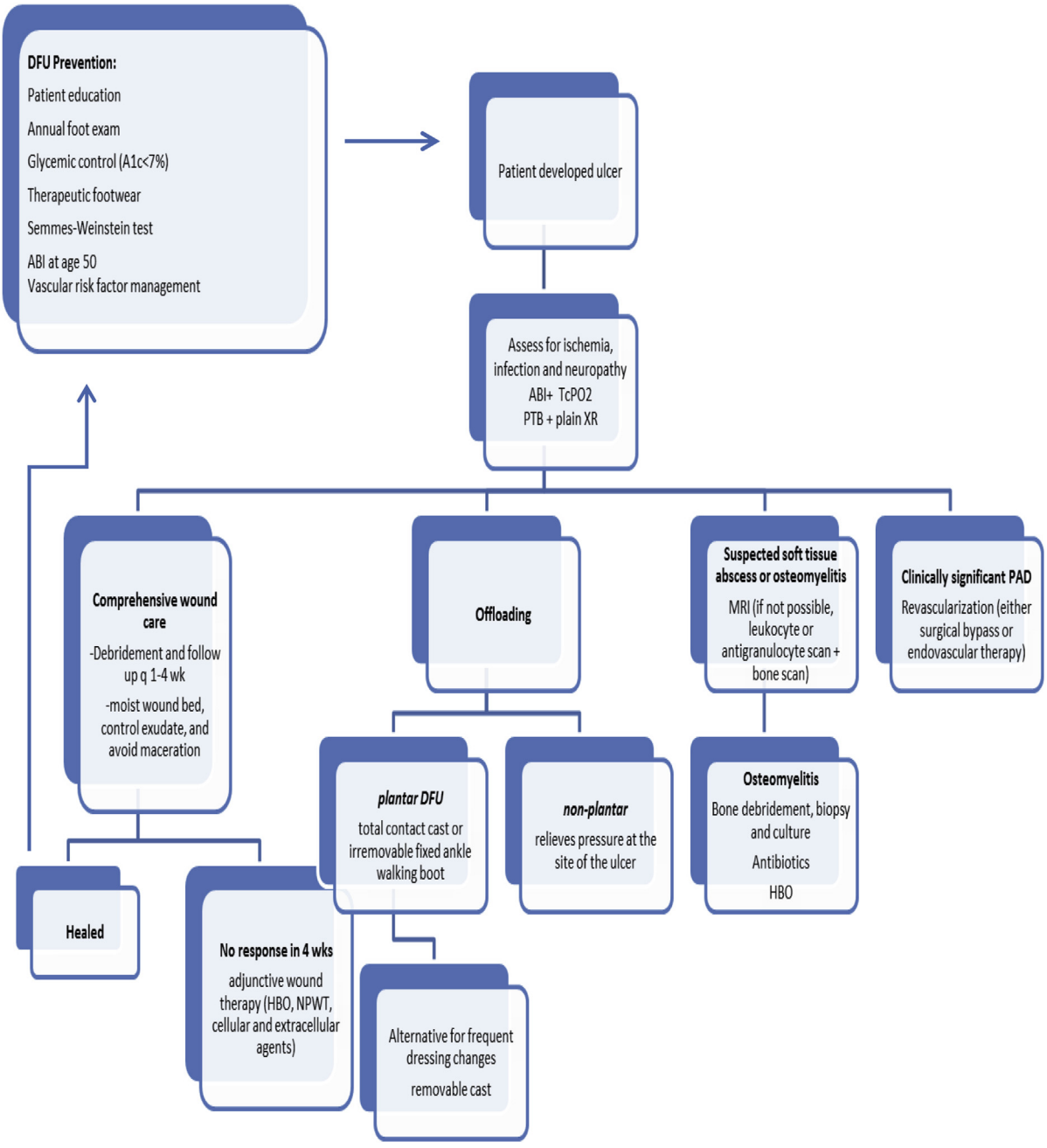

Fig. Algorithm for prevention and care of diabetic foot. *ABI,* Ankle-brachial index; *DFU,* diabetic foot ulcer; *HBO,* hyperbaric oxygen; *MRI,* magnetic resonance imaging; *NPWT,* negative pressure wound therapy; *PAD,* peripheral arterial disease; *PTB,* probe to bone; *$TcPo_2$,* transcutaneous oxygen pressure; *XR,* radiography.

document" that will be modified as techniques are further refined, technology develops, medical therapy improves, and new data emerge. The committee monitored the literature for new evidence emerging after the search of the five commissioned systematic reviews, and the group periodically updated guidelines as new data became available.

To provide clinicians with a comprehensive guide on the management of DFU, the committee reviewed several relevant guidelines from other organizations and societies (American Diabetes Association and IDSA)[17,18] and adapted several evidence-based recommendations from these guidelines. An algorithm that summarizes the prevention and care of the DFU is depicted in the Fig.

1. Prevention of diabetic foot ulceration

Recommendation 1. We recommend that patients with diabetes undergo annual interval foot inspections by physicians (MD, DO, DPM) or advanced practice providers with training in foot care (Grade 1C).

Evidence. The frequency of visits should be based on the patient's predefined risk for foot problems but should probably be on at least a yearly basis. A history of prior foot ulceration or amputation and a history of poor visual acuity should be evaluated.[9] The examination should include testing for neuropathy (Semmes-Weinstein monofilament)[19] and palpation of pedal pulses; foot deformity (hammer or claw toes, bunions, or Charcot deformities) should be assessed to include the presence of pressure points and callus formation. Examination of the toes, including between the toes for fissures and calluses and nail problems, should be done.[20] Important history elements to elucidate include current patient foot care practices, how often, and what is done. We recommend basic patient education about foot care and periodic reinforcement, although patient compliance with therapies rather than education has been demonstrated to have the greatest influence on reducing foot ulceration and amputation.[21,22]

During the course of evaluating patients, those determined to be at increased risk (presence of neuropathy, ischemia, anatomic deformity) should have more frequent foot evaluations by foot specialists and increased reinforcement of direct patient education.

Whereas the ABI is the "gold standard" test for limb blood flow, toe pressures are often better to use in diabetic persons, given the frequency of medial arterial calcification. Overall, ABI or toe-brachial index confers a sensitivity of 63% and a specificity of 97% in detecting hemodynamically significant PAD. At least limited evidence suggests that toe blood pressures may be useful in predicting not only the potential for wound healing but also the risk of ulceration.[9]

Although several risk stratification schemes have been proposed, a simple four-level system for follow-up has been developed by the American College of Foot and Ankle Surgeons (Table) and appears appropriate.[9]

Recommendation 2. We recommend that foot examination include testing for peripheral neuropathy using the Semmes-Weinstein test (Grade 1B).

Evidence. Peripheral neuropathy is one of the primary causes of diabetic foot problems, with 45% to 60% of DFUs being purely neuropathic in origin.[9] In comparison to those with intact sensation, patients with neuropathy are at a >3.5-fold increased risk for recurrent ulceration.[23] The presence of sensory neuropathy with a foot deformity further increases the risk of foot ulceration.

Several methods for assessing peripheral neuropathy include the tuning fork test, a neurothesiometer, and the Semmes-Weinstein 10-g monofilament test. The last test is thought to be most accurate and involves a monofilament sensory stimulation at defined areas on the foot and over the first toe and first, third, and fifth metatarsal areas. The examiner elicits a yes or no response from the patient to the pressure of the filament. The recommended frequency of this test is empirical, but yearly with the primary care provider examination is reasonable. The evidence supporting that use of this test modifies practice is scant. However, patients with severe neuropathy as assessed by this test have both an increased risk of DFU and greater risk of limb loss. Patients identified as having significant neuropathy should be considered for increased interval examinations as well as for customized orthotic footwear.

Table. Suggested frequency for follow-up evaluation

Category	*Risk profile*	*Evaluation frequency*
0	Normal	Annual
1	Peripheral neuropathy	Semiannual
2	Neuropathy with deformity and/or PAD	Quarterly
3	Previous ulcer or amputation	Monthly or quarterly

PAD, Peripheral arterial disease.

Recommendation 3. We recommend education of the patients and their families about preventive foot care (Grade 1C).

Evidence. Educating the patients and their family about proper foot care makes empirical sense and is likely cost-effective. This education can be provided by a physician, podiatrist, or skilled health care practitioner providing dedicated education time to explain the basics of the care of the foot, callus, and nail and fitting of shoes. This education should be done during the patient's yearly foot inspection examination, usually after completion of the history and examination portion of the visit. Plain speaking and allowing questions are important.

Studies specifically evaluating education interventions are few and provide low-level evidence, with only modest improvement in outcome.[24,25] A very small conceptual intensive psychosocial intervention showed reduced risk behavior for DFU development.[26] Ambulation exercise with weight-bearing program showed benefits to those at risk with diabetes and neuropathy, but hard outcomes of ulcer occurrence were not reported.[27]

Recommendation 4.

a. We suggest against the routine use of specialized therapeutic footwear in average-risk diabetic patients (Grade 2C).
b. We recommend using custom therapeutic footwear in high-risk diabetic patients, including those with significant neuropathy, foot deformities, or previous amputation (Grade 1B).

Evidence. Diabetes is associated with a high incidence of foot disorders leading to plantar pressure, and repetitive trauma resulting from improper footwear is a frequent contributor to DFUs.[9] Approximately half of

diabetes-related amputations in the United States have been attributed to improper footwear.

Proper well-fitted footwear should decrease the risk of calluses and toe deformities. In combination with a quality athletic walking shoe, custom foot orthoses have been shown to decrease plantar pressures but have no significant impact on foot pain in diabetics.[28] The data regarding the efficacy of custom diabetic footwear with respect to prevention of ulceration are mixed. A small Italian trial including 69 patients reported reulceration in 28% of patients treated with therapeutic shoes in comparison to 58% in the control group.[29] However, in a larger randomized trial including 400 patients with a healed ulcer, there was no difference in reulceration at 2 years among those randomized to therapeutic shoes with custom cork inserts (15%), therapeutic shoes with prefabricated polyurethane inserts (14%), and usual footwear (17%).[23] Therapeutic shoes did not appear to be protective even among those with foot insensitivity. However, this study failed to include patients with significant foot deformities or with a previous amputation, and the advantages of therapeutic footwear in this population remain unknown.

The routine prescription of therapeutic footwear cannot be recommended over a preventive foot care program in low-risk diabetic patients. However, patients should be provided with sufficient information to guide selection of appropriate footwear while avoiding dangerous shoes. A study of 400 diabetic patients with a history of healed ulceration showed that 50% of women and 27% of men wore shoes classified as dangerous (shallow or narrow toe box, no laces, open toes or heels, or heel height placing undue pressure on the ball of the foot) at some point during the day.[30] Recommended footwear should include a broad and square toe box, laces with three or four eyes per side, padded tongue, quality lightweight materials, and sufficient size to accommodate a cushioned insole.[31] In-shoe orthotic inlays are effective in preventing ulceration as assessed by a Cochrane review.[32]

Most trials have excluded high-risk diabetic patients, including those with significant foot deformities or previous amputation or ulcers, and there may be a role for custom shoes in these populations. In one study of 117 patients, custom footwear was successful in reducing peak pressure points in patients at high risk of DFU, but hard outcomes of ulceration were not reported.[33] However, a recent large randomized controlled trial (RCT) in 298 high-risk patients with custom orthoses and foot care compared with routine care found a 48% reduction in incident ulcers at 5 years ($P < .0001$).[34] Other guidelines suggest prescription of protective footwear in diabetic patients with arterial disease, significant neuropathy, previous ulcer or amputation, callus formation, or foot deformity.[35] We suggest that therapeutic footwear be considered in these high-risk populations.

Recommendation 5. We suggest adequate glycemic control (hemoglobin $A_{1c} < 7\%$ with strategies to minimize hypoglycemia) to reduce the incidence of DFUs and infections, with subsequent risk of amputation (Grade 2B).

Evidence. Several large trials have suggested survival benefit and lower overall morbidity with tight glycemic control. For example, the UK Prospective Diabetes Study (UKPDS) showed that intensive glycemic control decreased mortality and microvascular complications compared with standard regimens.[36] Assessment in these studies included limb loss and revascularization. No major differences were found with macrovascular complications, but benefits were found for peripheral neuropathy. The SVS commissioned comprehensive systematic review and meta-analysis[37] of nine trials enrolling 19,234 patients. Compared with less intensive glycemic control, intensive control (hemoglobin A_{1c}, 6%-7.5%) was associated with a significant decrease in risk of amputation (relative risk [RR], 0.65; 95% confidence interval [CI], 0.45-0.94; $I^2 = 0\%$). Intensive control was significantly associated with slower decline in sensory vibration threshold (mean difference, −8.27; 95% CI, −9.75 to −6.79). There was no effect on other neuropathic changes (RR, 0.89; 95% CI, 0.75-1.05; $I^2 = 32\%$) or ischemic changes (RR, 0.92; 95% CI, 0.67-1.26; $I^2 = 0\%$).

High-risk patients may not gain as much benefit as lower risk patients, probably because of irreversible changes that occur late in the disease. As with many chronic diseases, tight glycemic control relies much on patient compliance long term to prevent DFU. Last, evidence exists that hemoglobin A_{1c} may be a useful marker for DFU healing; in a study of 183 patients with DFU, every increase of 1% in glycosylated hemoglobin decreases wound healing rate by 0.028 cm/d.[38]

Recommendation 6. We recommend against prophylactic arterial revascularization to prevent DFU (Grade 1C).

Evidence. No trials have been done specifically addressing this question, but given the inherent pattern of long-segment and distal arterial disease often present in diabetes, risks of the invasive procedures, and induced vascular injury by endoluminal and open revascularization, the benefit is not apparent. Both open surgical bypass and endovascular revascularization can have significant short-term and long-term complications.[39]

Indications for arterial revascularization should be based on the standard indications of severe claudication, rest pain, and tissue loss.[40] Primary foot ulcerations in diabetic neuropathy are unlikely to be directly related to impaired large-artery blood flow; rather, they are related to abnormal gait and foot weight distribution. As noted in Recommendation 1, assessment to evaluate ischemia as a factor contributing to development or nonhealing of ulceration is essential. Moreover, the neuropathy of diabetes is not primarily ischemic in nature, and there is no evidence that revascularization reverses ischemic neuropathy except in the setting of acute ischemia.

Conversely, for patients with diabetes and tissue loss in the setting of significant PAD, revascularization to prevent limb loss is well justified (Grade 1B).[40] The specific use of endovascular vs open surgical revascularization in diabetes-associated PAD is beyond the scope of this review.

2. Off-loading DFUs

Recommendation 1. In patients with plantar DFU, we recommend off-loading with a total contact cast (TCC) or irremovable fixed ankle walking boot (Grade 1B).

Recommendation 2. In patients with DFU requiring frequent dressing changes, we suggest off-loading using a removable cast walker (RCW) as an alternative to TCC and irremovable fixed ankle walking boot (Grade 2C). We suggest against using postoperative shoes or standard or customary footwear for off-loading plantar DFUs (Grade 2C).

Recommendation 3. In patients with nonplantar wounds, we recommend using any modality that relieves pressure at the site of the ulcer, such as a surgical sandal or heel relief shoe (Grade 1C).

Recommendation 4. In high-risk patients with healed DFU (including those with a prior history of DFU, partial foot amputation, or Charcot foot), we recommend wearing specific therapeutic footwear with pressure-relieving insoles to aid in prevention of new or recurrent foot ulcers (Grade 1C).

Evidence. Off-loading diabetic foot wounds is a key component of care and is an essential management strategy.[9,41-44] Because most plantar ulcers result from repetitive or high plantar pressures, it therefore follows that such pressures must be ameliorated or reduced to allow healing to occur.[45] Similarly, many lesions occurring on nonplantar surfaces can be attributed to pressure from tight footwear or constricting bandages. Accordingly, these offending pressures must also be eliminated to ensure healing. Although not the sole component of care for DFUs, pressure reduction (off-loading) must occur in conjunction with any other basic or advanced wound therapy.[9,35,44,46-48] Once healed, prevention of recurrent or new ulcers must be a priority for ongoing care of high-risk feet, including those with previous partial foot amputation. Numerous guidelines and publications therefore recommend the provision of protective footwear with pressure-relieving insoles as a primary prevention strategy in this regard.[9,33,41,42,49-54] Unfortunately, there is often a lack of adherence to off-loading strategies on the part of affected patients as well as a disconnect between guideline recommendations and clinical practice.[41,42,51,55,56]

Numerous off-loading modalities have been reported for DFUs, including TCCs, braces, RCWs, irremovable cast walkers (often referred to as instant TCCs [iTCCs]), half-shoes, modified surgical shoes, foot casts, and various felt or foam dressings.[42,43,51,57-69] Whereas each device has its advantages for any given patient, almost any off-loading modality is superior to no off-loading for the management of DFUs.[43] For many years, the TCC has been considered the most effective off-loading modality for DFUs by virtue of its pressure redistribution properties as well as irremovability.[42,70,71] An early small trial by Mueller et al[63] in 1989 showed superiority of TCC over standard wound care and accommodative footwear in healing of DFUs. Significantly, 90% of TCC-treated ulcers healed in a mean time of 42 days compared with 32% of the traditional dressing group that healed in a mean of 65 days ($P < .05$). Several other prospective studies have also confirmed the clinical efficacy of the TCC in healing of DFUs.[58,66,71-74] Although not as effective in healing of ulcers, removable devices such as cast walkers and half-shoes have also become popular for off-loading DFUs.[58,75] Patient adherence to the continual use of the devices is less than optimal, making their removability a likely detriment to ulcer healing.[76] Recognizing this, Armstrong et al[57] performed a 12-week randomized trial comparing ulcerated patients treated with an irremovable cast walker (iTCC) with a group randomized to an RCW. As hypothesized, a significantly higher proportion of patients healed in the iTCC group than in the RCW group (82.6% [19 patients] vs 51.9% [14 patients]; $P = .02$; odds ratio, 1.8; 95% CI, 1.1-2.9). With confirmation that the irremovable device performed significantly better than that which was removable, the next obvious question was whether the iTCC could perform as well as the TCC in healing DFUs during a similar 12-week time frame. In the same month, Katz et al[64] published the results of their RCT comparing these two irremovable devices. In an intention-to treat analysis, the proportions of patients with ulcers that healed in 12 weeks in the TCC and iTCC groups were 74% and 80%, respectively ($P = .65$). Healing times were also nonsignificantly different, with median healing times of 5 weeks and 4 weeks in the TCC and RCW groups, respectively. This was followed by several other studies using different but similar irremovable RCWs, each showing nonsignificant differences in rates of healing and healing times.[62,68,71] Subsequently, most recent DFU clinical trials and guidelines have recommended that irremovable devices be used as preferred off-loading modalities for plantar DFUs.[9,35,44,53,77]

Once healed, these patients must be prescribed therapeutic footwear with pressure-relieving insoles to prevent recurrent or new foot lesions.[9,41,42,52,78] In-shoe plantar pressure analysis can be useful in identifying high-pressure locations for customization of insoles and footwear.[33,49] Several prospective studies have demonstrated that patients wearing prescriptive pressure-relieving footwear have significantly fewer recurrences of ulceration compared with those persons not wearing therapeutic shoes.[29,79] The same is true for all high-risk patients, including those with a prior history of DFU, partial foot amputations, or Charcot foot.[9] Such patients have higher than normal plantar pressures because of underlying structural deformities or biomechanical perturbations (often secondary to peripheral neuropathy).[80-82] Whereas surgical off-loading can be beneficial in properly selected patients,[83] these deformities and high plantar pressures need to be ameliorated with appropriate footwear.[9,41,51] Unfortunately, patient adherence to wearing of prescription footwear is often insufficient and requires further attention to reduce the risk for reulceration.[41,56]

The SVS commissioned a systematic review[84] to evaluate the different off-loading methods. Their findings and those of a Cochrane systematic review[43] were

consistent and highlighted that the quality of the current evidence is somewhat low and the available trials are small with several limitations. The review summarized 19 interventional studies, of which 13 were RCTs, including data from 1605 patients with DFUs using an off-loading method. The quality of the included studies ranges from low to moderate. This analysis demonstrated improved wound healing with total contact casting over RCW, therapeutic shoes, and conventional therapy. There was no advantage of irremovable cast walkers over total contact casting. There was improved healing with half-shoe compared with conventional wound care. Therapeutic shoes and insoles reduced relapse rate in comparison with regular footwear. Data were sparse regarding other off-loading methods.

3. Diagnosis of diabetic foot osteomyelitis (DFO)

The diagnosis of DFO relies heavily on the correlation between the clinical, histologic, and imaging studies presented in the individual patient. Foot infection is the most frequent diabetic complication requiring hospitalization and the most common precipitating event leading to lower extremity amputation.[85,86] The mal perforans ulcer plays a pivotal role as the major predisposing factor to infection in the diabetic foot. This type of ulceration is commonly a result of persistent trauma and repeated plantar pressure on the insensate foot. The breakdown of the skin leads to the increased probability of wound infection that can subsequently lead to deep tissue infection and inevitably include bone infiltration that results in the presence of contiguous osteomyelitis. The key underlying risk factors that contribute to the development of DFIs are neuropathy, vasculopathy, and, to a lesser extent, immunopathy.[86] Diagnosis and treatment of osteomyelitis are viewed as the most challenging and controversial aspects of managing this infectious process.[87] DFO may be present in up to 20% of mild to moderate infections and in 50% to 60% of severely infected wounds.[88] One of the most difficult aspects of diagnosing DFO is differentiating it from Charcot neuroarthropathy, which is noninfectious and may often coexist in the presence of a DFU and an insensate foot. Although the pathophysiologic mechanism of osteomyelitis seen in the diabetic patient in the presence of an ulcer is better and more clearly understood than in previous years, the systematic treatment regimen is still not well defined. The literature supports the role of an interdisciplinary team as well as a multimodality approach to the DFI to improve outcomes and to decrease amputation rates.[86] In the arena of classification of a wound infection and the severity and outcome of treatment of a DFI, there is no empirical evidence that one classification system (Meggit-Wagner, PEDIS [perfusion, extent/size, depth/tissue loss, infection, and sensation], SAD/SAD [size (area, depth), sepsis, arteriopathy, and denervation], SINBAD [site, ischemia, neuropathy, bacterial infection, area, and depth], or UT [University of Texas]) or one wound score (USI, DUSS [Diabetic Ulcer Severity Score], MAID [palpable pedal pulses (I), wound area (A), ulcer duration (D), and presence of multiple ulcerations (M)], or DFI Wound Score) is better than any other.[89] The multimodal approach involving clinical evaluation, laboratory testing, and a stepwise approach to imaging modalities is the best way to confirm and to determine the best treatment regimen for the patient with DFO.

The following section presents recommendations and evidence consistent with the most current IDSA guidelines on the diabetic foot.[18]

Recommendation 1. In patients with a DFI with an open wound, we suggest doing a probe to bone (PTB) test to aid in diagnosis (Grade 2C).

Evidence. PTB has fair sensitivity and specificity for diagnosis of osteomyelitis (60% and 91%, respectively)[90] and high positive predictive value (89%)[91] in patients with high pretest probability of disease. The accuracy in patients at lower pretest probability is lower.[87] PTB has only fair reproducibility among examiners.[92] PTB is inexpensive and poses minimal risk to the patient. Therefore, it is helpful in ruling in osteomyelitis, but when the result is negative, additional testing is needed to rule out the condition. The quality of this evidence is low as it mainly consists of small observational studies that did not measure the impact of test results on patient outcomes but rather provided diagnostic accuracy measures.

Recommendation 2. In all patients presenting with a new DFI, we suggest that serial plain radiographs of the affected foot be obtained to look for bone abnormalities (deformity, destruction) as well as soft tissue gas and radiopaque foreign bodies (Grade 2C).

Evidence. Plain radiographs of the foot have relatively low sensitivity and specificity for confirming or excluding osteomyelitis with a fair sensitivity and specificity (54% and 68%, respectively) and low diagnostic odds ratio of 2.84, suggesting low to moderate accuracy.[90,92] Radiographic findings are only marginally predictive of osteomyelitis if positive and even less predictive of the absence of osteomyelitis if negative.[93]

The quality of this evidence is low as there are no specific studies identified that included obtaining and monitoring of sequential plain radiographs over time. Clinicians might consider using serial plain radiographs to diagnose or to monitor suspected DFO, with evidence that changes in radiologic appearance during an interval of at least 2 weeks are more likely to predict the presence of osteomyelitis than a single radiographic study.[18]

Recommendation 3. For those patients who require additional (ie, more sensitive or specific) imaging, particularly when soft tissue abscess is suspected or the diagnosis of osteomyelitis remains uncertain, we recommend using MRI as the study of choice. MRI is a valuable tool for diagnosis of osteomyelitis if the plain film is not useful (Grade 1B).

Evidence. The pooled sensitivity and specificity of MRI for DFO were excellent (90% and 79%, respectively), with the diagnostic odds ratio of 24.4 indicating excellent discriminant power.[90] More recently performed studies reported lower diagnostic odds ratios compared with the

older ones, with a possible explanation that the more recent study designs were perhaps better.[94]

The quality of evidence supporting the use of MRI in DFO is moderate to high. The meta-analysis included four large prospective studies, with two of the four using consecutive recruitment, although only one was recent.[90,94] MRI is generally considered the best of the currently available advanced imaging technique options for diagnosis of osteomyelitis. Limitations of using MRI include the limited availability of radiologists with expertise in musculoskeletal images, limited availability, and high cost. Differentiating osteomyelitis from Charcot neuroarthropathy remains challenging. The risk of MRI to patients is minimal.[18]

Recommendation 4. In patients with suspected DFO for whom MRI is contraindicated or unavailable, we suggest a leukocyte or antigranulocyte scan, preferably combined with a bone scan as the best alternative (Grade 2B).

Evidence. Nuclear medicine scans have a high sensitivity but a relatively low specificity (especially bone scans). The pooled sensitivity and specificity were 81% and 28%, respectively, with the pooled diagnostic odds ratio of 2.10, which indicated poor discriminating ability. The accuracy for detection of osteomyelitis using nuclear medicine bone scan and indium-labeled leukocyte scans is in general low to moderate.[90] Although the combination of bone scanning and labeled leukocyte scan provides the best scanning accuracy outside of MRI, it remains labor-intensive and costly, and it is still not as specific as MRI.

Recommendation 5. In patients at high risk for DFO, we recommend that the diagnosis is most definitively established by the combined findings on bone culture and histology (Grade 1C). When bone is débrided to treat osteomyelitis, we recommend sending a sample for culture and histology (Grade 1C).

Evidence. The literature provides only a limited number of studies that examined clinical examination techniques for diagnosis of DFO, making it difficult to produce robust estimates. More studies are needed to give enough data for predictive values.

Recommendation 6. For patients *not* undergoing bone débridement, we suggest that clinicians consider obtaining a diagnostic bone biopsy when faced with diagnostic uncertainty, inadequate culture information, or failure of response to empirical treatment (Grade 2C).

Evidence. Cultures of bone specimens provide more accurate microbiologic data than soft tissue for determining the presence of DFO and have been shown to provide greater accuracy as to the specific organisms causing the infection; therefore, the treatment can be more tailored for better treatment outcome. A retrospective multicenter study demonstrated that patients who underwent bone culture-guided antibiotic treatment had a significantly better outcome.[90]

4. Wound care for DFUs

Attentive care to the diabetic foot wound requires frequent inspection with irrigation and débridement, protective dressings, infection and inflammation control, and plantar off-loading.[9,18,35,48,95] These components are essential to preserve a moist, noninfected wound environment that will progress through granulation and epithelialization to full healing in a timely manner.

Evaluation and initial treatment of diabetic foot wounds. ***Recommendation 1.*** We recommend frequent evaluation at 1- to 4-week intervals with measurements of diabetic foot wounds to monitor reduction of wound size and healing progress (Grade 1C).

Evidence. Percentage reduction in wound size is an early predictor of treatment outcome.[35,96-99] Wound area reduction of 10% to 15% per week or ≥50% area reduction in 4 weeks results in increased likelihood of healing with decreased complications of infection and amputation. Although there are no studies that evaluated the benefits and utility of different wound check intervals, studies that monitored healing progression of DFUs strongly correlated 50% healing at 4 weeks with final full healing by 16 weeks. By measuring wounds at 1- to 4-week intervals, the clinician documents healing progress and identifies the basis for treatment modification.

Recommendation 1.1

We recommend evaluation for infection on initial presentation of all diabetic foot wounds, with initial sharp débridement of all infected diabetic ulcers, and urgent surgical intervention for foot infections involving abscess, gas, or necrotizing fasciitis (Grade 1B).

Recommendation 1.2

We suggest that treatment of DFIs should follow the most current guidelines published by the IDSA (Ungraded).

Evidence. Diagnosis and management of DFIs have been systematically addressed with IDSA evidence-based clinical practice guidelines.[18] On careful review of the most current IDSA clinical practice guideline, this committee notes that the scope and depth of these recommendations represent the most current standard of care for management of DFIs.

Wound dressings. ***Recommendation 2.*** We recommend use of dressing products that maintain a moist wound bed, control exudate, and avoid maceration of surrounding intact skin for diabetic foot wounds (Grade 1B).

Evidence. Dressings are used to provide a favorable wound environment for healing. A moist wound bed for open wounds is the well-documented standard of care and supported by evidence-based guidelines.[35,48,95,100] Optimal wound care provides moist coverage, absorption of exudate, autolytic débridement, prevention of infection, and promotion of granulation. Nonadherent dressings that protect the wound bed are standard treatment for most wounds.

There is little quality evidence to support the use of any single dressing product over another in promoting a moist wound bed for the DFU.[35,48,95,101-103] Cochrane reviews of RCTs with meta-analysis for hydrogels,[104] hydrocolloids,[105] foam dressings,[106] and alginates[107] found insufficient evidence to support any one of these dressing groups over another for acceleration of wound healing. There is

minimal evidence for increased rate of healing with other popular wound dressings, including honey[108-110] and topical silver.[111-114] There is limited evidence that hyaluronic acid-containing products are associated with positive effects on wound healing compared with standard products.[115] Numerous trials of variable quality targeting therapy for DFUs have been challenged by inadequate sample size, difficulty in follow-up, nonrandomization of treatment arms, nonblinded outcome assessment, and concurrent multiple interventions.[116] Heterogeneity of the population and multiple variables regarding both the person and the wound limit trial design and implementation.

As individual wounds differ in their properties, dressing selection should be based on the characteristics of the wound, cost, and ease of use. Dry wounds benefit from hydrogels and hydrocolloids to preserve moisture. Foam dressings and alginates absorb drainage and are preferred for exudative wounds. Consideration should be made to change a product if wound area reduction fails to meet recommended guidelines (Recommendation 1). Adverse effects such as maceration, infection, or further loss of tissue should prompt a change in wound dressing modality. With respect to cost, standard dressings that have longer wearing times, do not require trained personnel for application, maintain adherence to the skin but nonadherence to the wound bed, and are comfortable may result in less overall expenditure for product purchase.

Débridement of diabetic foot wounds. ***Recommendation 3.*** We recommend sharp débridement of all devitalized tissue and surrounding callus material from diabetic foot ulcerations at 1- to 4-week intervals (Grade 1B).

Evidence. Standard or "good" wound care for DFUs has long been defined to include daily dressing changes, sharp débridement of ulcer, systemic control of any present infection, and off-loading of pressure.[35,48,95,100,117] Débridement of DFUs allows drainage of exudate and removal of nonviable tissue, thus reducing infection by decreasing bacterial burden. It permits valid assessment of the wound size, depth, and characteristics and encourages healing. Removal of surrounding callus material reduces pressure load on the wound.[118] Débridement intervals are patient customized, dependent on production rate of exudates and presence of devitalized tissue.

Recommendation 4. Considering lack of evidence for superiority of any given débridement technique, we suggest initial sharp débridement with subsequent choice of débridement method based on clinical context, availability of expertise and supplies, patient tolerance and preference, and cost-effectiveness (Grade 2C).

Evidence. Débridement methods include surgical (sharp or standard), larval therapy, hydrotherapy, ultrasound, hydrogel, various occlusive dressings, and enzymatic.[117] Wet-to-dry dressings, in which saline-soaked gauze is allowed to dry on the wound then physically ripped off, were a past standard mechanical débridement technique. These have fallen out of favor as the débridement is nonselective, harming viable tissue in addition to removal of necrotic debris, and may be painful.[119]

In examining controlled studies on various methods of débridement, the quality of evidence remains fair to moderate. The SVS commissioned systemic review[120] of 13 interventional studies (10 RCTs and three nonrandomized studies), including data from 788 patients. The risk of bias in the included studies was moderate. Meta-analysis of three RCTs showed that autolytic débridement significantly increased healing rate compared with standard wound débridement (RR, 1.89; 95% CI, 1.35-2.64). Meta-analysis of four comparative studies (one RCT) showed that larval débridement reduced amputation (RR, 0.43; 95% CI, 0.21-0.88) but not complete healing (RR, 1.27; 95% CI, 0.84-1.91). No significant difference in wound healing was found between autolytic débridement and larval débridement (one RCT). Surgical débridement had shorter healing time compared with conventional wound care (one RCT). Ultrasound débridement was associated with reduction in wound size compared with surgical débridement. Hydrosurgical débridement had similar wound healing outcomes to standard surgical débridement.

In general, comparative effectiveness evidence was of low quality, and the débridement method is recommended to be at the clinician's discretion, with the goal of wound size reduction to full healing. The chosen débridement method should encourage patient compliance with the overall care plan.

Indications for adjunctive therapies. ***Recommendation 5.*** For DFUs that fail to demonstrate improvement (>50% wound area reduction) after a minimum of 4 weeks of standard wound therapy, we recommend adjunctive wound therapy options. These include negative pressure therapy, biologics (PDGF, living cellular therapy, extracellular matrix products, amnionic membrane products), and hyperbaric oxygen therapy. Choice of adjuvant therapy is based on clinical findings, availability of therapy, and cost-effectiveness; there is no recommendation on ordering of therapy choice. Re-evaluation of vascular status, infection control, and off-loading is recommended to ensure optimization before initiation of adjunctive wound therapy (Grade 1B).

Evidence. Adjunctive therapies for the healing of DFUs should be considered after all standard of care measures have been implemented.[44,96-99,121] Standard, comprehensive care should include wound off-loading, local wound débridement, control of edema, control of bioburden, and wound moisture balance with appropriate dressings. Standard of care for diabetic foot ulcerations will lead to improvement in the majority of cases, and only in those cases without improvement should adjunctive modalities be used. The cost of these therapies can be high, and the evidence supporting their use is not sufficiently strong to justify their use as primary therapy without an attempt at lower cost, evidence-based methods. Failure to demonstrate improvement after 4 weeks of treatment should lead the clinician to reassess the adequacy of and compliance with débridement/wound care, proper off-loading of the DFU, and adequacy of the arterial perfusion of the foot before considering adjunctive treatment

options. Re-evaluation of the patient and wound should be performed before the use of adjuvant therapies to ensure that offloading is implemented, bioburden is well controlled, vascular supply is optimized, and exudate is not excessive.

The SVS commissioned a systematic review[121] to evaluate the efficacy of three adjunctive therapies: hyperbaric oxygen therapy, arterial pump devices, and pharmacologic agents (pentoxifylline, cilostazol, and iloprost). They identified 18 interventional studies, of which nine were randomized, enrolling 1526 patients. The quality of the included studies ranged from low to moderate. Arterial pump devices had a favorable effect on complete healing in one small trial compared with hyperbaric oxygen therapy and in another small trial compared with placebo devices. Neither iloprost nor pentoxifylline had a significant effect on amputation rate compared with conventional therapy. No comparative studies were identified for cilostazol in DFUs. Evidence was most supportive for hyperbaric oxygen therapy.

Recommendation 6. We suggest the use of negative pressure wound therapy (NPWT) for chronic diabetic foot wounds that do not demonstrate expected healing progression with standard or advanced wound dressings after 4 to 8 weeks of therapy (Grade 2B).

Evidence. NPWT is safe and effective treatment for DFUs. A multicenter RCT (n = 342) demonstrated NPWT to be as safe as and more efficacious than advanced moist wound therapy (AMWT) for DFUs.[122] Patients treated with NPWT healed to closure faster, experienced significantly fewer secondary amputations, and required significantly fewer home care therapy days than patients treated with AMWT.

Other RCTs and studies demonstrated reduced time to complete healing of DFUs, reduced duration and frequency of hospital admission, and decreased rate of amputation compared with AMWT/débridement[123]; decreased healing time and improved quality of life[124]; increased rate of appearance of granulation tissue[125]; reduced length of hospitalization and reduced amputation rates with functional residual extremity[126]; reduced time to granulation, clearing of bacterial infection, and successful granulation[127]; and significant reduction in wound size compared with conventional therapy.[127] Systematic reviews[35,48,102,128-131] summarized recommendations with moderate to strong evidence for use of NPWT in DFUs. Retrospective analysis of reimbursement claims demonstrated reduced numbers of amputations in NPWT groups vs traditional therapies, regardless of depth of wound,[132] and more rapid successful wound treatment end point and decreased resource utilization due to reduction in nursing visits.[133] Consideration of high cost of NPWT products and access to trained personnel for application of NPWT dressings should be weighed in choosing this treatment modality.

Recommendation 7. We suggest consideration of the use of PDGF (becaplermin) for the treatment of DFUs that are recalcitrant to standard therapy (Grade 2B).

Evidence. Although multiple growth factors have been studied in clinical trials, to date, only PDGF has been approved by the Food and Drug Administration for the treatment of DFUs.[134-136] Becaplermin (Regranex) is a recombinant human BB isoform of PDGF suspended in a gel designed for topical application. PDGF has a central role in the stimulation of tissue regeneration by promoting angiogenesis through macrophage secretion of vascular endothelial growth factor (VEGF), fibroblast activity, and epithelial migration. Becaplermin is applied daily to the DFU and covered with saline-moistened gauze. It has been studied clinically in four prospective, randomized, placebo-controlled trials. In a meta-analysis of these studies, Smiell et al[137] aggregated the 922 patients studied for analysis. Four groups were identified: patients treated with a standard regimen of good ulcer care and wet-to-dry gauze dressings, those treated with good ulcer care plus placebo gel, and those treated with good ulcer care plus becaplermin gel at two different doses. Fifty percent of ulcers treated with the higher dose of becaplermin for 20 weeks healed, compared with 36% treated with placebo gel ($P = .007$). Adverse events were rare, and the only medication-related event was local tissue sensitivity in 2%.

Multiple cost-efficacy analyses have been performed on the use of becaplermin to treat DFUs. Kantor and Margolis[138] studied 26,599 patients from a clinical wound treatment database and reported effective wound closure at 20 weeks in 31% of those treated with standard care compared with 43% treated with becaplermin. The incremental cost of increasing the odds of healing by 1% over standard therapy was $36.59 for becaplermin. Studies from Canada and Sweden also found becaplermin to be cost-effective therapy for the treatment of DFUs. In 2008, the Food and Drug Administration released a black box warning concerning the risk of fatal cancers in patients treated with becaplermin. Based on long-term follow-up studies of patients enrolled in randomized studies, there was no increased risk of malignancy in patients treated with becaplermin, but those who developed malignant neoplasms had a greater risk of dying of them.[139] This information is based on a small number of observations, so it should be interpreted with caution. It does emphasize, however, that the drug should be considered only in refractory DFUs failing to respond to standard therapy.

Recommendation 8. We suggest consideration of living cellular therapy using a bilayered keratinocyte/fibroblast construct or a fibroblast-seeded matrix for treatment of DFUs when recalcitrant to standard therapy (Grade 2B).

Evidence. Apligraf (Organogenesis, Canton, Mass) is a cultured bilayer skin substitute originating from neonatal foreskin.[140] A bovine collagen lattice is used as a base to support the organization of dermal fibroblasts and epithelial cells seeded after expansion of the separated neonatal cells. A layer of allogeneic keratinocytes is cultured over the fibroblast layer to form a stratified epidermis. The bilayer has a structure similar to human skin, with the absence of hair follicles or sweat glands. The growth factors and cytokines secreted by the cellular components of Apligraf

include fibroblast growth factor, VEGF, PDGF, transforming growth factor β, and multiple interleukins, paralleling those secreted by healthy human skin. The product requires a well-granulated wound bed in which exudate and bacterial levels have been controlled to yield positive results.

Apligraf was studied in a prospective randomized multicenter trial for the treatment of DFUs.[141] At 24 centers, 208 patients were treated with standard DFU care (débridement, foot off-loading) and saline-moistened gauze or standard DFU care and Apligraf application. After 12 weeks of treatment, 56% of Apligraf-treated wounds were closed, compared with 38% in the control group. The odds ratio for complete healing was 2.14 (95% CI, 1.23-3.74). The incidence of osteomyelitis was significantly less frequent in Apligraf-treated patients (2.7%) than in controls (10.4%; $P = .04$). Ipsilateral toe or foot amputation was also significantly less frequent in the Apligraf group (6.3%) than in the control group (15.6%). Cost-effectiveness analysis revealed 12% reduction in costs during the first year of treatment compared with standard wound care alone.[142] The increased ulcer-free time coupled with a reduced risk of amputation to a large extent offset the initial costs of the product.

Dermagraft. Dermagraft (Organogenesis) is an allogeneic dermal fibroblast culture derived from human neonatal foreskin samples and grown on a biodegradable scaffold.[143] The resulting three-dimensional matrix can be implanted into chronic nonhealing wounds to supply functional fibroblasts and their corresponding expressed proteins. The scaffold biodegrades during a 1- to 2-week period, leaving behind only cellular components and proteins. Several in vitro studies have evaluated the ability of Dermagraft to express clinically significant quantities of growth factors after cryopreservation and thawing. VEGF, PDGF-A, and insulin-like growth factor I were all found to recover to significant levels as measured by enzyme-linked immunosorbent assay in wounds to which Dermagraft was applied.

The pivotal study of Dermagraft in DFUs was a single-blinded, randomized, controlled investigation at 35 centers enrolling 314 patients comparing standard DFU care with standard care plus the weekly application of Dermagraft for up to 8 weeks.[144] Clinical studies evaluating Dermagraft and Apligraf were not double blinded because the unique characteristics of the devices preclude the use of a placebo that cannot be distinguished from the true product. Standard care in both groups consisted of routine sharp débridement, pressure off-loading, and saline-moistened gauze dressings. Of the 314 patients enrolled, 245 evaluable patients completed the study. Results showed that treatment with Dermagraft produced a significantly greater proportion (30%) of healed ulcers compared with the control group (18%). The number of ulcer-related adverse events (local wound infection, osteomyelitis, cellulitis) was significantly lower in the Dermagraft-treated patients (19%) than in the control patients (32%; $P = .007$). Similar findings were noted in a smaller clinical trial (n = 28) with more ulcers closed, faster closure, higher percentage of ulcers closed by week 12, and fewer infections than in the control patients.[145]

Recommendation 9. We suggest consideration of the use of extracellular matrix products employing acellular human dermis or porcine small intestinal submucosal tissue as an adjunctive therapy for DFUs when recalcitrant to standard therapy (Grade 2C).

Evidence. A variety of tissue constructs have recently become available, approved through the 510K mechanism as adjunctive therapies for the healing of chronic wounds including DFUs. This includes products incorporating human tissue (acellular dermis, amniotic membrane, cryopreserved skin, others) or animal tissue (bladder tissue, pericardial tissue, intestinal submocosa). Of the multitude of these products, only two have been found to provide benefit compared with standard DFU treatment. A porcine small intestinal submucosa (SIS) construct (OASIS; Cook Biotech, West Lafayette, Ind) has been tested in a prospective randomized trial. In this study, 73 patients with DFUs were randomized to treatment with standard care and SIS compared with standard care and becaplermin. More wounds in the SIS-treated group healed at 12 weeks (49% vs 28% treated with becaplermin; $P = .055$). Although it is not statistically superior to treatment with PDGF, it seems reasonable to consider the use of SIS, given the previous trials demonstrating improved healing rates with becaplermin compared with standard DFU therapy.

An acellular human dermal matrix (Graftjacket; Wright Medical Technology, Memphis, Tenn) was studied in a prospective randomized multicenter trial in 87 patients with DFUs compared with standard care. Significantly more wounds treated with the human dermal matrix healed at 12 weeks (69.6%) than with control (46.2%; $P = .03$).[146,147]

It must be stressed that these adjunctive therapies are not a substitute for the standard principles of wound healing. If the wound is not well prepared before application of a growth factor or living tissue substitute, there is little potential for wound stimulation or accelerated healing. Strict wound off-loading is required for maximum benefit.

Recommendation 10. In patients with DFU that fails to respond to 4 to 6 weeks of conservative management, we suggest hyperbaric oxygen therapy (Grade 2B).

Evidence. The SVS-commissioned systematic review[121] demonstrated that hyperbaric oxygen therapy improves wound healing and reduces the risk of amputation. In multiple randomized trials, hyperbaric oxygen therapy was associated with increased healing rate (Peto odds ratio, 14.25; 95% CI, 7.08-28.68) and reduced amputation rate (Peto odds ratio, 0.30; 95% CI, 0.10-0.89) compared with conventional therapy. Several other systematic reviews showed similar results. Considering the cost and the burden of prolonged daily treatment, patients should be selected for this therapy carefully. Using transcutaneous oximetry values can help stratify patients and predict those who are most likely to benefit.[148]

5. PAD and the DFU

Recommendation 1.1. We suggest that patients with diabetes have ABI measurements performed when they reach 50 years of age (Grade 2C).

Recommendation 1.2. We suggest that patients with diabetes who have a prior history of DFU, prior abnormal vascular examination, prior intervention for peripheral vascular disease, or known atherosclerotic cardiovascular disease (eg, coronary, cerebral, or renal) have an annual examination of the lower extremities and feet including ABI and toe pressures (Grade 2C).

Recommendation 2. We recommend that patients with DFU have pedal perfusion assessed by ABI, ankle and pedal Doppler arterial waveforms, and either toe systolic pressure or transcutaneous oxygen pressure ($TcPo_2$) annually (Grade 1B).

Evidence. DFUs are a common, costly, and complex complication of diabetes. One in four patients with diabetes will develop a foot ulcer during his or her lifetime.[149] DFUs are important because of their negative impact on quality of life, contribution to increased mortality, and strong link with major limb amputation.[150] Up to 85% of major limb amputations in patients with diabetes are preceded by foot ulcers.[5]

DFUs are multifactorial and are generally categorized as neuropathic, neuroischemic, and ischemic. There are strong data to suggest that the pathophysiologic mechanism of DFUs has changed during the last 20 years, with an increasing proportion of ischemic and neuroischemic ulcers. It is currently estimated that at least 65% of DFUs have an ischemic component, nearly double that reported in the early 1990s.[150,151] This change has important implications in provision of care and outcomes analysis because patients with ischemic ulcers suffer from a higher recurrence rate, double the amputation rate, and inferior maintenance of independence and ability to ambulate compared with patients with neuropathic ulcers.[152]

The relationship of diabetes and PAD is complex. Diabetes is a major risk factor for PAD, and depending on its definition, PAD prevalence rates are 10% to 40% among the general population of patients with diabetes.[151] The combination of diabetes and PAD is a sinister one, with an associated 5-year mortality rate approaching 50%, higher than for many forms of cancer.[150] The mortality of a patient with PAD and diabetes who suffers an amputation is 50% at 2 years.

Clearly, identification and comprehensive medical management of PAD in patients with diabetes are important. In addition, in patients with DFUs, PAD should be identified and graded,[153] and if it is contributing to delayed healing or nonhealing of the ulcer, it should be corrected by endovascular or open surgical means as appropriate. The mere presence of PAD in a DFU patient, defined as an ABI of <0.8, is associated with an increased risk of limb loss.[154] More profound degrees of ischemia increase the risk of limb loss.[152,155]

The incidence of PAD in people with diabetes appears to have significantly increased during the last two decades.[156-159] In addition, the proportion of patients with diabetes and wounds who have ischemic or neuroischemic wounds has increased compared with neuropathic wounds alone.[156,157]

The American Diabetes Association recommends that all people with diabetes have ABI measurements performed when they reach 50 years of age,[17] and all people with diabetes and a foot wound should have pedal perfusion assessed by ABI and either toe pressure or $TcPo_2$.[160] ABI <0.8 increases amputation risk in the presence of a foot wound in a patient with diabetes.[154] Diminishing degrees of perfusion increase amputation risk, especially when ABI is <0.4 and toe systolic pressure is <30 mm Hg.[161,162] "Subcritical" degrees of ischemia need to be considered and may warrant intervention in a patient with diabetes and a foot wound who does not respond to adequate offloading and débridement.

The systematic review[163] commissioned by the SVS to support these guidelines demonstrated that several tests are available to predict wound healing in the setting of diabetic foot; however, most of the available evidence evaluates only $TcPo_2$ and ABI. $TcPo_2$ may be a more predictive test than ABI, but both tests predicted healing and the risk of amputation. ABI measurements may be falsely elevated in a significant number of patients with diabetes because of medial calcinosis. Toe Doppler arterial waveforms and pressures are helpful in such patients, and alternative perfusion measurements may be especially applicable to patients with foot wounds; a spectrum of ischemia may help quantify the degree of ischemia, including pulse volume recordings, skin perfusion pressures, and quantitative indocyanine green angiography.

Recommendation 3. In patients with DFU who have PAD, we recommend revascularization by either surgical bypass or endovascular therapy (Grade 1B).

Recommendation 3 (technical and implementation remarks).

- Prediction of patients most likely to require and to benefit from revascularization can be based on the SVS WIfI lower extremity threatened limb classification.
- A combination of clinical judgment and careful interpretation of objective assessments of perfusion along with consideration of the wound and infection extent is required to select patients appropriately for revascularization.
- In functional patients with long-segment occlusive disease and a good autologous conduit, bypass is likely to be preferable.
- In the setting of tissue loss and diabetes, prosthetic bypass is inferior to bypass with vein conduit.
- The choice of intervention depends on the degree of ischemia, the extent of arterial disease, the extent of

the wound, the presence or absence of infection, and the available expertise.

Evidence. The choice of endovascular therapy (EVT) first vs surgical bypass for patients with tissue loss, PAD, and diabetes is currently much debated.[155] A recent comprehensive evidence-based review could find no clear evidence favoring EVT vs open bypass.[151] There has been a clear trend toward more widespread application of EVT first,[164] but no randomized trials have been performed in patients with diabetes. Retrospective studies suggest that EVT results in more repeated interventions and perhaps lower healing rates, particularly in patients with long-segment occlusive disease and more advanced tissue ischemia (gangrene vs ulcer).[165] At least in the United States, the amputation rate for patients with DFUs has stabilized or begun to decline[166]; increased rates of vascular intervention (angiography, EVT, and open bypass) are associated with this decline.[167] A balanced view would acknowledge that both EVT and open autologous vein bypass are important means of revascularization as part of a comprehensive approach to functional limb salvage in patients with diabetes, lower extremity wounds, and diabetes.[168,169] It is presently unclear for which patients EVT is preferable to open bypass. There are data suggesting that the outcomes of EVT for TransAtlantic Inter-Society Consensus type D femoropopliteal lesions are poor in patients with diabetes. In functional patients with a good autologous conduit, bypass is likely to be preferable in this cohort.[155] In the setting of tissue loss and diabetes, prosthetic bypass is distinctly inferior to bypass with vein conduit.[170] For the wide spectrum of other patients with diabetes or ulceration and gangrene with variable degrees of arterial insufficiency, the choice of intervention likely depends on the degree of ischemia, the extent of arterial disease, the extent of the wound, the presence or absence of infection, and the expertise of the practitioner.[171]

A final important point relates to the DFU complicated by PAD with superimposed infection. The risk of amputation in a patient with a DFU correlates directly with increasing infection severity. Infection is especially deleterious in patients with diabetes and PAD; in fact, PAD plus infection tripled the likelihood of nonhealing in the Eurodiale study.[6,172] Aggressive control of infection with appropriate antibiotics and timely, thorough débridement as well as prompt revascularization once infection is controlled are keys to managing this cohort of difficult patients.[172] Therefore, after drainage of infection, revascularization should be strongly considered if a diabetic foot wound does not promptly respond to standard wound care in accordance with the SVS WIfI system.[6,172-174]

AUTHOR CONTRIBUTIONS

Conception and design: AH, GL, PH, MM, LL, KZ, VD, RF, WM
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Statistical analysis: Not applicable
Obtained funding: Not applicable
Overall responsibility: AH

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Submitted Jun 5, 2015; accepted Oct 8, 2015.

A systematic review and meta-analysis of glycemic control for the prevention of diabetic foot syndrome

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Objective: **The objective of this review was to synthesize the available randomized controlled trials (RCTs) estimating the relative efficacy and safety of intensive vs less intensive glycemic control in preventing diabetic foot syndrome.**
Methods: **We used the umbrella design (systematic review of systematic reviews) to identify eligible RCTs. Two reviewers determined RCT eligibility and extracted descriptive, methodologic, and diabetic foot outcome data. Random-effects meta-analysis was used to pool outcome data across studies, and the I^2 statistic was used to quantify heterogeneity.**
Results: **Nine RCTs enrolling 10,897 patients with type 2 diabetes were included and deemed to be at moderate risk of bias. Compared with less intensive glycemic control, intensive control (hemoglobin A_{1c}, 6%-7.5%) was associated with a significant decrease in risk of amputation (relative risk [RR], 0.65; 95% confidence interval [CI], 0.45-0.94; $I^2 = 0\%$). Intensive control was significantly associated with slower decline in sensory vibration threshold (mean difference, −8.27; 95% CI, −9.75 to −6.79). There was no effect on other neuropathic changes (RR, 0.89; 95% CI, 0.75-1.05; $I^2 = 32\%$) or ischemic changes (RR, 0.92; 95% CI, 0.67-1.26; $I^2 = 0\%$). The quality of evidence is likely moderate.**
Conclusions: **Compared with less intensive glycemic control therapy, intensive control may decrease the risk of amputation in patients with diabetic foot syndrome. The reported risk reduction is likely overestimated because the trials were open and the decision to proceed with amputation could be influenced by glycemic control. (J Vasc Surg 2016;63:22S-28S.)**

Diabetic foot syndrome arises from either vasculopathic or neuropathic complications of diabetes.[1] Prevalence varies from 3% to 30% among patients with diabetes.[2] Diabetic foot syndrome leads to an ulcer in 10% to 30% of patients.[3-5] It increases the risk of amputation by 8- to 23-fold and increases mortality rates in patients with diabetes.[3-5] Complicated foot ulcers represent a major reason for hospitalization, amputation, and utilization of health care resources.[1]

It has been postulated that chronic hyperglycemia is associated with microvascular and macrovascular changes that play a role in diabetic foot disease.[6,7] However, it is yet unclear whether lowering glucose to normal or nearly normal targets (intensive glycemic control) leads to reduction in the incidence of diabetic foot syndrome (ie, prevention of diabetic foot). This hypothesis has been tested in several randomized controlled trials (RCTs) that reported variable findings. The United Kingdom Prospective Diabetes Study (UKPDS)[7] concluded that intensive control had a favorable effect on the incidence of microvascular complications and diabetic foot but not on macrovascular disease. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[8] showed similar effect on microvascular events but reported an increase in total and cardiovascular-related mortality and increased weight gain. The Veterans Affairs Cooperative Study on type 2 diabetes mellitus (VA CSDM)[9] demonstrated that intensive control had no significant effect compared with conventional control, and it did not decrease the overall prevalence of peripheral neuropathy.

Therefore, we conducted this systematic review and meta-analysis to appraise and to summarize the randomized trial evidence regarding the impact of intensive glycemic control on the incidence of amputation and other diabetic foot syndrome outcomes.

METHODS

Because glycemic control can be achieved by multiple interventions and in multiple settings and because its effect has been evaluated previously in multiple systematic reviews, we used an umbrella systematic review approach.

From the Evidence-based Practice Center,[a] Mayo Clinic Libraries,[d] Division of Endocrinology, Diabetes, Metabolism, and Nutrition,[g] and Division of Preventive, Occupational and Aerospace Medicine,[h] Mayo Clinic, Rochester; the Department of Internal Medicine, University of Missouri, Columbia[b]; the Unidad de Conocimiento y Evidencia (CONEVID), Lima[c]; the Department of Surgery, University of Michigan Medical School, Ann Arbor[e]; and the Second Medical Department, Aristotle University Thessaloniki, Thessaloniki.[f]
This review was partially funded by a contract from the Society for Vascular Surgery.
Author conflict of interest: none.
Additional material for this article may be found online at www.jvascsurg.org.
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Independent peer review and oversight have been provided by members of the Society for Vascular Surgery Document Oversight Committee: Peter Gloviczki, MD (Chair), Martin Bjorck, MD, Ruth Bush, MD, Thomas Forbes, MD, Michel Makaroun, MD, and Gregory Moneta, MD.
0741-5214

http://dx.doi.org/10.1016/j.jvs.2015.10.005

In brief, this approach starts with identifying relevant systematic reviews that compared intensive glycemic control with less intensive control. Eligible systematic reviews are retrieved (regardless of intervention and regardless of whether diabetic foot was an outcome of interest) and are used to identify relevant RCTs. RCTs are subsequently retrieved and undergo quality appraisal, data extraction, and meta-analysis of relevant outcomes.

Information sources and search methods. A comprehensive literature search was conducted by an expert reference librarian with input from study investigators with experience in systematic reviews (V.M.M. and M.H.M.). We searched the electronic databases (MEDLINE, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials [CENTRAL]) for systematic reviews using various combinations of controlled vocabulary supplemented by keywords for the concepts of prevention and diabetic foot. Results were limited to systematic reviews. The full search strategy is reported in the Appendix (online only).

Two reviewers working independently identified systematic reviews eligible for further review by performing a screen of abstracts and titles. If a systematic review was deemed relevant, the manuscript was obtained and reviewed in full-text versions. The included RCTs from the reviewed systematic reviews were retrieved in full-text versions (all available versions of each study) for further assessment.

Eligibility criteria. We included RCTs that enrolled patients with diabetes (of any type) without diabetic foot ulcers, comparing intensive glycemic control against less intensive glycemic control and evaluating the incidence of diabetic foot syndrome. The outcomes of interest were amputation and the incidence of diabetic foot, defined as a new ulcer, gangrene, or other forms of neuropathic or ischemic changes.

Risk of bias assessment. We used the Cochrane risk of bias tool to evaluate the methodologic quality of RCTs. Two reviewers independently assessed trial quality by examining several components: generation of allocation sequence (classified as adequate if based on computer-generated random numbers, tables of random numbers, or similar), concealment of allocation (classified as adequate if based on central randomization, sealed envelopes, or similar), blinding (patients, caregivers, or outcome assessors), baseline imbalance, adequacy of follow-up, and source of funding (whether it is only by not-for-profit sources or includes for-profit source). Disagreements between the reviewers were resolved by discussion or arbitrated with a third reviewer (M.H.M.). The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methods.[10,11] Following this approach, randomized trials are considered to warrant high-quality evidence (ie, high certainty) and observational studies warrant low-quality evidence. Then the evidence grading can be increased (if a large effect is observed) or decreased if other factors are noted, such as studies being at increased risk of bias or imprecise (small with wide confidence intervals [CIs]).

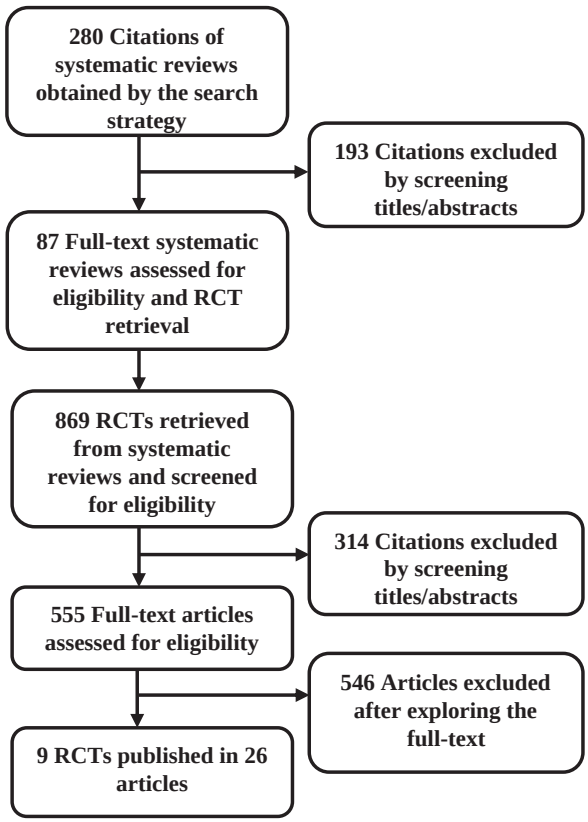

Fig 1. The process of study selection. *RCTs,* Randomized controlled trials.

Data collection and extraction. The data from RCTs were extracted using a standardized, piloted, and web-based data extraction form and working in duplicates. We abstracted data on patient demographics, baseline characteristics, study design, sample size, intervention type, fasting blood glucose and hemoglobin A_{1c} levels, and diabetic foot outcome measures. The number of events in each trial was extracted, when available, and attributed to the arm to which patients were randomized (ie, the basis of the intention-to-treat approach). When change-from-baseline standard deviations for an outcome were not available, they were imputed from other studies in the review. When a study reported follow-up at different periods, outcomes with the longest follow-up were extracted.

Statistical analysis and data synthesis. We estimated the relative risk (RR) and the mean difference with the associated 95% CIs and pooled across studies using a random-effects model, as described by DerSimonian and Kacker.[12] We chose the random-effects method as primary analysis because of its conservative summary estimate and incorporation of between- and within-study variance. The analysis was repeated using the fixed-effect method, and discrepancies, if present, were outlined. To assess

Table I. Trial description and baseline characteristics

Trial	*Origin*	*No. of subjects*	*Follow-up, months*	*Duration of DM, years*	*Male, No. (%)*	*Age, years*	*Target in intensive group*	*Fasting glucose, mg/dL*		*HbA$_{1c}$, %*	
								At entry	*Achieved*	*At entry*	*Achieved*
VADT,[19] 2009	United States	1791	67.2	11.5	1737 (97)	61 ± 9	HbA$_{1c}$ <6%	—	—	I: 9.4 C: 9.4	I: 6.9 C: 8.4
Steno-2,[20] 2008	Denmark	160	46	I: 5.5 C: 6	118 (74)	55	HbA$_{1c}$ <6.5%	I: 182 C: 189	I: 130 C: 178	I: 8.4 C: 8.8	I: 7.9 C: 9.0
Holman,[21] 1983	United Kingdom	74	24	19	67 (64)	42 ± 12	PPG: 72-126	—	—	I: 11.7 C: 11.8	I: 10.5 C: 11.4
UKPDS,[7] 1998	United Kingdom	4209	120	0	2516 (60)	I: 53 ± 9 C: 53 ± 9	FPG <108	I: 146 C: 144	I: 155 C: 177	I: 7.1 C: 7.1	I: 8.1 C: 8.7
Abraira,[18] 1997 (VA CSDM)	United States	153	27	7.8	153 (100)	60 ± 6	HbA$_{1c}$ <7.5%	I: 207 C: 225	I: 103 C: 206	I: 9.3 C: 9.5	I: 7.1 C: 9.6
Ohkubo,[23] 1995	Japan	110	72	8.5	54 (49)	50 ± 16	HbA$_{1c}$ <7%	I: 165 C: 170	I: 125 C: 170	I: 9.2 C: 9.0	I: 7.1 C: 9.6
UGDP,[22] 1978	United States	619	120	1	177 (29)	53 ± 11	FPG <110	C: 143 I: 138	C: 166 I: 122	—	—
ADDITION-Europe,[16] 2011	United Kingdom and Denmark	3057	64		57	60	HbA$_{1c}$ <7%	—	—	I: 7.0 C: 7.0	I:6.6 C: 6.7
Araki,[17] 2012	Japan	1133	72	18	46	72	HbA$_{1c}$ <6.9%	170	—	8.5	I: 7.7 C: 7.8

C, Control; *DM*, diabetes mellitus; *FPG*, fasting plasma glucose; *HbA$_{1c}$*, hemoglobin A$_{1c}$; *I*, intervention; *PPG*, postprandial glucose.

heterogeneity of treatment effect among trials, we used the I^2 statistic; the I^2 statistic represents the proportion of heterogeneity of treatment effect across trials that is not attributable to chance or random error. Hence, a value of 50% reflects significant heterogeneity that is due to real differences in study populations, protocols, interventions, or outcomes.[13] The *P* value threshold for statistical significance was set at .05 for effect sizes. Analyses were conducted using features on RevMan version 5.1 (The Nordic Cochrane Center, Copenhagen, Denmark). The study was reported in accordance with the recommendations set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) work groups.[14]

RESULTS

Search results and study description. A total of 280 systematic reviews were identified by the electronic search strategy, of which 87 full-text articles met the eligibility for assessment. All RCTs included in eligible systematic reviews, whether their outcomes were pooled in a meta-analysis or not, were retrieved and screened for eligibility. A recent Cochrane systematic review[15] identified two RCTs[16,17] published after our search that we added to analysis. A total of nine RCTs, reported in 26 published manuscripts at different follow-up points, met the inclusion criteria.[7,16-23] We excluded several RCTs that are well known in this field. For the lack of planned glycemic control target, we excluded PROspective pioglitAzone Clinical Trial In macroVascular Events [PROactive][24] and the Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy trial (ADOPT).[25] For the lack of reporting amputation outcome, we excluded the ACCORD trial,[8] the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE),[6] and the RCT by Service et al.[26]

Fig 1 depicts the results of the search strategy, and Table I describes the included studies.

The nine trials enrolled 10,897 patients with diabetes. In these trials, patients were observed for a period of 2 years to 10 years (median, 5 years). Mean age ranged from 41 to 72 years; duration of diabetes before enrollment ranged from newly diagnosed to 19 years. The RCTs aimed for different glycemic targets for the intensive and the less intensive control arms. The goal of glycemic control was based on fasting glucose concentration of <126 mg/dL in the older trials and hemoglobin A$_{1c}$ (6%-7.5%) in more recent trials. Most included trials enrolled patients without known history of peripheral vascular disease who are at lower risk for amputation. All the trials that evaluated the outcome of amputation enrolled patients with type 2 diabetes (none with type 1). In Table I, we describe the characteristics of the trials; in Table II, we describe the intervention and control employed in each trial.

The standard domains of the risk of bias (Table III) were all adequate and consistent with low risk of bias with the exception of a concern about whether the decision to amputate was associated with the assignment to the intervention. It is plausible that patients with suboptimal control were more likely to be advised to proceed with amputation. Therefore, this evidence likely warrants moderate confidence.

Table II. Interventions used in included trials

Study ID	*Intensive arm*	*Conventional arm*
VADT,[19] 2009	Metformin plus rosiglitazone if BMI ≥27; glimepiride plus rosiglitazone if BMI <27; insulin was added if HbA_{1c} >9%. Patients started on the maximal dose.	Metformin plus rosiglitazone if BMI ≥27; glimepiride plus rosiglitazone if BMI <27; insulin was added if HbA_{1c} >9%. Patients started on half the maximal dose.
Steno-2,[20] 2008	If patients were unable to maintain HbA_{1c} <6.5% by means of diet and increased physical activity alone after 3 months, an oral hypoglycemic agent was started: • Overweight patients (BMI >25) received metformin (maximum, 1 g twice daily). • Lean patients, or overweight patients who had contraindications to metformin therapy, received gliclazide (maximum, 160 mg twice daily). • As the second step, metformin was added to the regimen of lean patients and gliclazide to that of overweight patients if hyperglycemia was not controlled. If the HbA_{1c} exceeded 7.0% despite maximal doses of oral agents, the addition of NPH insulin at bedtime was recommended. The insulin dose was adjusted on the basis of the morning fasting blood glucose concentration.	Treatment according to the 1988 recommendations of the Danish Medical Association
Holman,[21] 1983	Patients used ultralente insulin as basal cover and soluble insulin at mealtimes; mean insulin dose, 0.77 ± 0.30 IU/kg	Patients continued their usual therapy; mean insulin dose, 0.81± 0.29 IU/kg
UKPDS,[7] 1998	Treatment with one of the following three agents was initiated: • One of the following sulfonylureas: chlorpropamide 100-500 mg, glibenclamide 2.5-20 mg, or glipizide 2.5-40 mg • Metformin up to 2550 mg, distributed in two doses a day • Insulin started on once-daily ultralente insulin or isophane insulin. If the daily dose was >14 U or premeal or bedtime home blood glucose measurements were >7 mmol/L, a short-acting insulin, usually soluble (regular) insulin, was added (basal/bolus regimen). All participants had to continue their assigned treatment as long as possible. Patients were changed to insulin therapy if marked hyperglycemia recurred.	Patients were treated initially with dietary modification. If marked hyperglycemia or symptoms occurred, patients were secondarily randomized to treatment with sulfonylurea or insulin or metformin therapy. The aim of fasting plasma glucose <15 mmol/L without symptoms was maintained.
Abraira,[18] 1997 (VA CSDM)	*Phase 1*: one injection of intermediate- or long-acting insulin in the evening. *Phase 2*: continued evening insulin with the addition of glipizide in step increment of 2.5 to 5 mg/wk until HbA_{1c} goal is achieved or the maximum dose is reached. *Phase 3*: discontinue glipizide and give two insulin injections a day. *Phase 4*: multiple daily injections.	One daily injection of insulin; if goal not achieved, a maximum of two daily insulin injections are given.
Ohkubo,[23] 1995	Administered insulin three or more times daily (rapid-acting insulin at each meal and intermediate-acting insulin at bedtime)	One or two daily intermediate-acting insulin injections
UGDP,[22] 1978	Insulin variables (U-80 Lente or other insulin)	Standard insulin (U-80 Lente Iletin insulin)
ADDITION-Europe,[16] 2011	Target of HbA_{1c} <7%, but change in antidiabetic medicine with HbA_{1c} >6.5%	Standard care
Araki,[17] 2012	Oral hypoglycemic drugs (sulfonylurea, biguanides, α-glucosidase inhibitors, and pioglitazone) or insulin therapy	Oral hypoglycemic agents/ standard care

BMI, Body mass index; *HbA_{1c}*, hemoglobin A_{1c}.

Meta-analysis. Compared with less intensive glycemic control, intensive control was associated with a statistically significant decrease in risk of amputation of diabetic foot (RR, 0.65; 95% CI, 0.45-0.94; I^2 = 0%). Results are depicted in Fig 2.

Two studies reported on sensory nerve function,[21,23] in which a measurement of the changes in vibration threshold from baseline was used. The pooled result showed, when using the fixed-effect model, that compared with conventional control, intensive control

Table III. Quality assessment and risk of bias

Study ID	*Randomization*	*Allocation concealment*	*Blinding*	*Baseline imbalances*	*Lost to follow-up, %*	*Source of funding*
VADT,[19] 2009	Yes; permuted-block design	Yes; study sites did not have access to patient codes	Yes; patients and caregivers	No	6.4	Includes for-profit sources
Steno-2,[20] 2008	Yes; method unclear	Yes; sealed envelopes	Yes; outcome assessors	No	6.8	Not-for-profit sources
Holman,[21] 1983	Yes; method unclear	Yes; sealed envelopes	Unclear	No	6.8	Not-for-profit sources
UKPDS,[7] 1998	Yes; computer generated	Yes; sealed envelopes	Yes; outcome assessors	No	None	Not-for-profit sources
Abraira,[18] 1997 (VA CSDM)	Unclear	Unclear	Unclear	No	None	Not-for-profit sources
Ohkubo,[23] 1995	Unclear	Unclear	Unclear	No	2.7	Not-for-profit sources
UGDP,[22] 1978	Yes; tables of random numbers	Yes; method unclear	Yes; outcome assessors and data analyst	No	0	Not-for-profit sources
ADDITION-Europe,[16] 2011	Yes, cluster randomization	Yes	Outcome assessors	No	Unclear	Includes for-profit sources
Araki,[17] 2012	Adequate	Yes	Outcome assessors	No	9	Not-for-profit sources

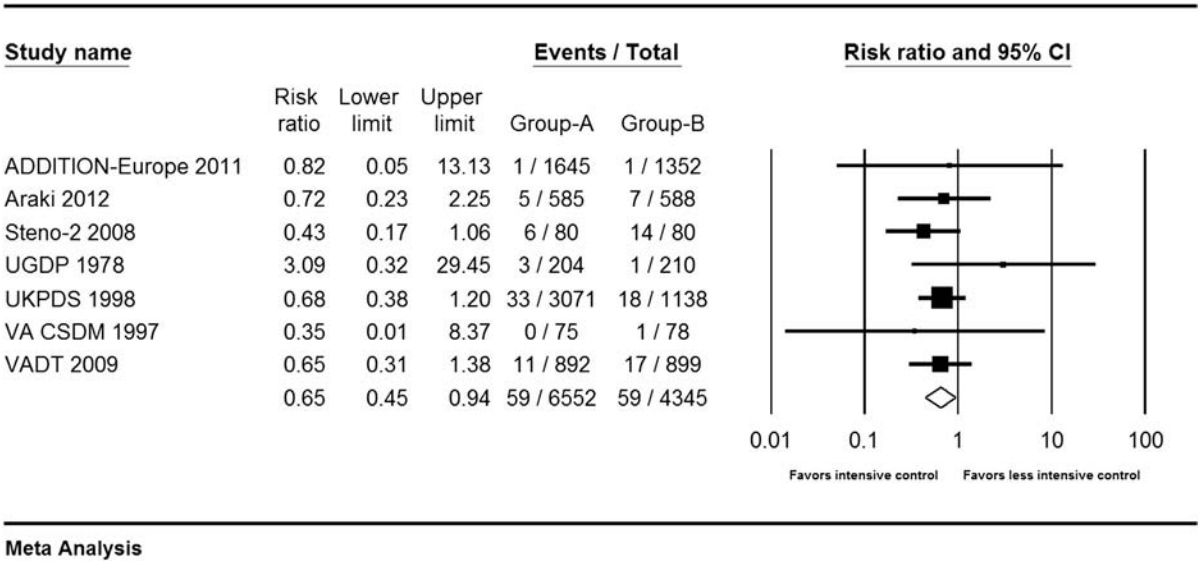

Fig 2. The risk of amputation. Group A, intensive control arm. Group B, conventional control arm. *CI,* Confidence interval.

caused a significant decrease (ie, less increase) in vibration threshold (mean difference, −8.27; 95% CI, −9.75 to −6.79), which means a better sensory nerve function outcome. The risk of neuropathic changes (RR, 0.89; 95% CI, 0.75-1.05; I^2 = 32%) and ischemic changes (RR, 0.92; 95% CI, 0.67-1.26; I^2 = 0%) associated with intensive glycemic control was not statistically significant (Supplementary Figs 1 and 2, online only). Ischemic changes were a heterogeneous outcome defined differently across trials (gangrene, ischemic ulcer, new-onset claudication, new diagnosis of peripheral artery disease). In metaregression, there was no significant association between the relative effect on amputation and the baseline risk for amputation in the control arms of the RCTs ($P > .05$). The small number of RCTs did not allow additional subgroup analyses or statistical evaluation for publication bias.

DISCUSSION

We conducted a systematic review and meta-analysis comparing intensive glycemic control with less intensive glycemic control for the prevention of diabetic foot. Intensive control was associated with decreased risk of amputation, better sensory nerve function, and potentially overall diabetic foot incidence. The quality of evidence is likely moderate, considering that these are open trials and the

decision to proceed with amputation may be associated with diabetes control, thus biasing the results toward favoring intensive glycemic control. Further, we were not able to assess certain confounders, such as baseline comparators of limb perfusion (eg, ankle-brachial index or toe-brachial index), medication use such as antiplatelet therapy, and personal habits of consistent foot hygiene. Most included trials enrolled patients without known history of peripheral vascular disease. The effect of diabetes control in patients with established peripheral vascular disease may be different, as these patients may be less responsive to intensive glucose control.

The observed RR reduction of 35% may indeed be too optimistic, considering the impact of other interventions, such as statins, smoking cessation, and blood pressure control. Intensive glycemic control may not improve patients' quality of life measures[27,28] and can be associated with increased treatment burden (more drugs, higher doses, more side effects, higher cost, more laboratory testing and visits to physicians). Thus, clinicians need to assess the capacity of the patient and the patient's caregivers to implement these complex programs.[29] Weight gain and hypoglycemia are common side effects associated with intensive control of type 2 diabetes.

Our results are consistent with those of a recent systematic review[15] of RCTs conducted by the Cochrane Collaboration. Our results are also consistent with a systematic review of observational prospective epidemiologic studies[30] that found a 1.26 RR (95% CI, 1.16-1.36) for each percentage point increase in hemoglobin A_{1c} to be associated with lower extremity amputation. The estimated RR was 1.44 (95% CI, 1.25-1.65) for type 2 diabetes and 1.18 (95% CI, 1.02-1.38) for type 1 diabetes; however, the difference was not statistically significant ($P = .09$).[30]

The strengths of this review stem from the comprehensive literature search that follows an explicit protocol and bias protection measures undertaken by reviewers (such as selecting studies, evaluating quality of the studies, and extracting outcome data by two independent reviewers). The weaknesses stem from inability to evaluate patient-level covariates that are needed to conduct meaningful subgroup analyses, such as cardiovascular risk factor control, use of statins and aspirin, age, and other comorbidities (eg, lower extremity edema). Such analyses may demonstrate differential benefit of an approach of intensive glycemic control.

The Society for Vascular Surgery is planning to develop clinical practice guidelines for the management of diabetic foot syndrome. A panel of experts will use data from this report and other sources of evidence and incorporate additional relevant aspects, such as patients' values and preferences, resource allocation, and clinical context, to develop clinical recommendations. A key factor in the recommendation for strict diabetes control is the need for it to be balanced with the potential for important hypoglycemia, the patient's capacity to achieve the glycemic control, and the risk of other outcomes, such as stroke and cardiovascular events, that can be associated with strict control of type 2 diabetes.

CONCLUSIONS

Compared with less intensive glycemic control therapy, intensive control decreases the risk of amputation in patients with diabetic foot syndrome. The reported risk reduction is likely overestimated because the trials were open and the decision to proceed with amputation could be influenced by glycemic control.

AUTHOR CONTRIBUTIONS

Conception and design: RH, BF, TE, JD, AT, LP, GP, MN, VM, MM
Analysis and interpretation: RH, MM
Data collection: RH, BF, TE, JD, AT, LP, GP, MN, MM
Writing the article: RH, LP, GP, VM, MM
Critical revision of the article: RH, BF, TE, JD, AT, LP, GP, MN, MM
Final approval of the article: RH, BF, TE, JD, AT, LP, GP, MN, MM
Statistical analysis: MM
Obtained funding: MM
Overall responsibility: MM

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Submitted Sep 8, 2015; accepted Oct 8, 2015.

Additional material for this article may be found online at www.jvascsurg.org.

APPENDIX (online only).

Data sources and search strategies

A comprehensive search of several databases from each database's earliest inclusive dates to October 2011 (any language, any population) was conducted. The databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid Embase, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principle investigator. Controlled vocabulary supplemented with keywords was used to search for the topic: diabetes control, limited to systematic reviews.

The actual search strategy

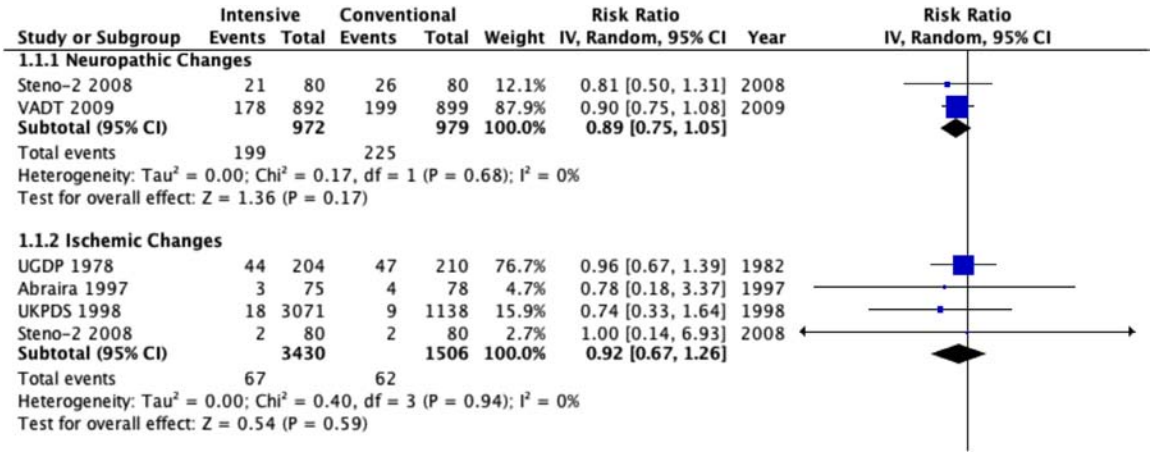
Ovid. Databases: Embase 1988 to 2011 Week 41, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present, EBM Reviews—Cochrane Database of Systematic Reviews 2005 to October 2011.

Search strategy:

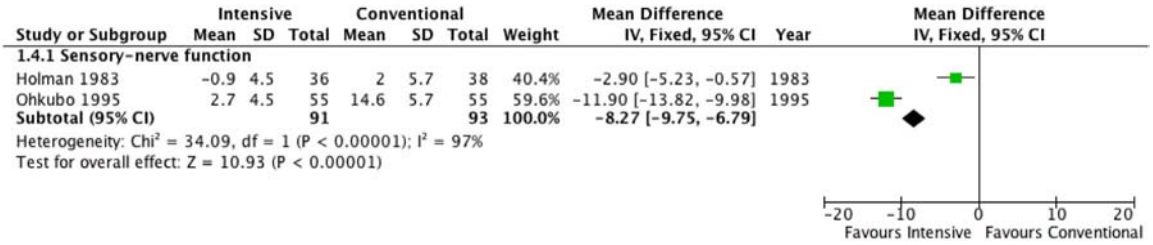
#	*Searches*	*Results*
1	exp Diabetes Mellitus/pc [Prevention & Control]	33286
2	(control or controls or controlling).ti,ab.	3743841
3	1 and 2	8728
4	(diabetes adj3 (control or controls or controlling)).ti,ab.	15376
5	exp "systematic review"/	44283
6	(systematic* adj2 review*).mp.	106172
7	3 or 4	22638
8	5 and 7	148
9	6 and 7	323
10	from 9 keep 203-323	121
11	from 7 keep 22621-22638	18
12	8 or 10 or 11	271
13	remove duplicates from 12	234
14	limit 13 to (book or book series or editorial or erratum or letter or note or addresses or autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CDSR; records were retained]	22
15	13 not 14	212
16	11 or 15	230

Scopus.

1) TITLE-ABS-KEY((control w/3 diabetes) or (controls w/3 diabetes) or (controlling w/3 diabetes))
2) TITLE-ABS-KEY(systematic* w/2 review*)
3) 1 and 2
4) PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
5) 3 and not 4
6) DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
7) 5 and not 6



Supplementary Fig 1 (online only). The risk of neuropathic and ischemic changes. *CI*, Confidence interval; *IV*, information value.



Supplementary Fig 2 (online only). Neuropathy; changes in vibration threshold (fixed-effect model). *CI*, Confidence interval; *IV*, information value; *SD*, standard deviation.

A systematic review and meta-analysis of tests to predict wound healing in diabetic foot

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Background: **This systematic review summarized the evidence on noninvasive screening tests for the prediction of wound healing and the risk of amputation in diabetic foot ulcers.**
Methods: **We searched MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Scopus from database inception to October 2011. We pooled sensitivity, specificity, and diagnostic odds ratio (DOR) and compared test performance.**
Results: **Thirty-seven studies met the inclusion criteria. Eight tests were used to predict wound healing in this setting, including ankle-brachial index (ABI), ankle peak systolic velocity, transcutaneous oxygen measurement ($TcPo_2$), toe-brachial index, toe systolic blood pressure, microvascular oxygen saturation, skin perfusion pressure, and hyperspectral imaging. For the $TcPo_2$ test, the pooled DOR was 15.81 (95% confidence interval [CI], 3.36-74.45) for wound healing and 4.14 (95% CI, 2.98-5.76) for the risk of amputation. ABI was also predictive but to a lesser degree of the risk of amputations (DOR, 2.89; 95% CI, 1.65-5.05) but not of wound healing (DOR, 1.02; 95% CI, 0.40-2.64). It was not feasible to perform meta-analysis comparing the remaining tests. The overall quality of evidence was limited by the risk of bias and imprecision (wide CIs due to small sample size).**
Conclusions: **Several tests may predict wound healing in the setting of diabetic foot ulcer; however, most of the available evidence evaluates only $TcPo_2$ and ABI. The overall quality of the evidence is low, and further research is needed to provide higher quality comparative effectiveness evidence. (J Vasc Surg 2016;63:29S-36S.)**

In 2010, there were 25.8 million people in the United States with diabetes.[1] As a major cause of morbidity, 15% of these patients would develop diabetic foot ulcers (DFUs) resulting from diabetic neuropathy or peripheral arterial disease.[2] Inappropriately treated or untreated DFUs can lead to severe consequences, including lower extremity amputation and even death.

Predicting wound healing is an essential step in the management of DFUs. It is estimated that early detection and appropriate treatments may prevent up to 85% of amputations.[3] A range of noninvasive tests have been proposed in the literature to predict wound healing, including ankle-brachial index (ABI), toe-brachial index (TBI), transcutaneous oxygen measurement ($TcPo_2$), and toe systolic blood pressure (TBP).

Other tests have also been studied. Because in ischemic limbs blood moves at a much slower velocity in distal leg arteries (compared with nonischemic limbs), one other test is the ankle peak systolic velocity (APSV), which is estimated as the mean of the peak velocities measured across the distal tibial artery at the ankle level.[4] Hyperspectral imaging is a noninvasive diagnostic tool that quantifies tissue oxygenation and generates anatomically relevant maps of microcirculatory changes. The map is based on local molecular composition (as reflected by wavelength selection) of molecules such as oxyhemoglobin and deoxyhemoglobin.[5] Microvascular oxygen saturation (Sao_2) can be measured using a micro-lightguide spectrophotometer that sends light from a xenon lamp to the tissue, where it is scattered and then collected by surrounding fibers. Light signal is converted into an electrical signal, digitized, and analyzed in real time by comparing to pre-recorded spectra of fully deoxygenated and oxygenated hemoglobin spectra.[6] Skin perfusion pressure (SPP) can be measured by a laser Doppler scanner that is secured in a blood pressure cuff with a transparent window and records perfusion pressure during deflation.[7]

However, it is unclear which test has the best prognostic accuracy in detecting treatment outcomes.

Hereby, we conducted a systematic review and meta-analysis to summarize the evidence of available tests and to compare the performance of eight noninvasive tests in

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This review was partially funded by a contract from the Society for Vascular Surgery.
Author conflict of interest: none.
Additional material for this article may be found online at www.jvascsurg.org.
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Independent peer review and oversight have been provided by members of the Society for Vascular Surgery Document Oversight Committee: Peter Gloviczki, MD (Chair), Martin Bjorck, MD, Ruth Bush, MD, Thomas Forbes, MD, Michel Makaroun, MD, and Gregory Moneta, MD.
0741-5214

http://dx.doi.org/10.1016/j.jvs.2015.10.004

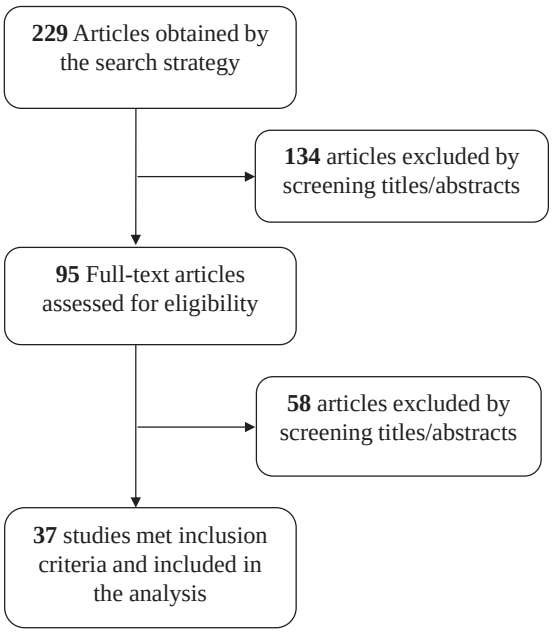

Fig 1. Study selection.

predicting wound healing of DFUs. To our knowledge, this is the first meta-analysis on this topic.

METHODS

The methodology and reporting of this systematic review are consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[8] The protocol of this systematic review was developed by the Society for Vascular Surgery Committee tasked to develop guidelines for the management of diabetic foot.

Study selection. To be eligible for this review, studies had to be clinical trials or observational studies that used one of these eight noninvasive tests: ABI, APSV, $TcPo_2$, TBI, TBP, microvascular Sao_2, SPP, and hyperspectral imaging. Studies had to report the incidence of subsequent healing of DFUs or the need for subsequent amputation. DFU patients, regardless of age, gender, ethnicity, and underlying symptoms, were included in analysis. Studies that reported only pretreatment test results were excluded, as were editorials, letters, errata, notes, and commentaries. Clinical reviews (systematic and nonsystematic reviews) and medical guidelines were used to identify relevant studies.

Literature search. We conducted a broad search of six electronic databases, including Ovid MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Scopus, from database inception to October 2011. The appropriate database search terms were developed for the concept of DFUs and for the concept of each noninvasive test. The search terms were broad without language or country restrictions. The detailed search strategy is available in the Appendix (online only).

Data abstraction. Two independent reviewers screened the study titles and abstracts using a predefined protocol. Full texts of the relevant studies were further assessed for inclusion by the same pair of reviewers. All discrepancies between the reviewers were resolved through consensus.

Two reviewers extracted study details independently, in duplicate, using a standardized pilot-tested form. The following data were abstracted: study design, patient characteristics (sex, age), sample size, diabetes type, baseline ulcer status, length of follow-up, tests, and outcomes. The outcomes of interest were the number of healed foot ulcers and the number of amputated limbs. The outcomes were extracted at the longest duration of complete follow-up. We extracted or calculated the number of healed vs nonhealed ulcers and amputated limbs vs nonamputated limbs and constructed contingency tables. Predefined thresholds were used (ABI, 0.8; $TcPo_2$, 30 mm Hg). When data reported were unclear, the authors of the included studies were contacted for clarification.

Risk of bias and methodologic quality assessment. Considering that the included studies were either nonrandomized or randomized for purposes other than the goal of this systematic review, we applied the Newcastle and Ottawa quality assessment tool and evaluated representativeness of study samples, exposure ascertainment, blinding of outcome assessors, and loss to follow-up.[9] The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methods.[10,11] Following this approach, randomized trials are considered to warrant high-quality evidence (ie, high certainty), and observational studies warrant low-quality evidence. Then the evidence grading can be increased (if a large effect is observed) or decreased if other factors are noted, such as studies being at increased risk of bias or imprecise (small with wide confidence intervals [CIs]).

Data synthesis. To evaluate the effectiveness of each test in predicting outcomes of interest, we calculated sensitivity and specificity for each test using bivariate binominal mixed models.[12,13] Developed by Reitsma et al and later refined by Chu and Cole, the bivariate binominal mixed model assumes independent exact binomial distributions of number of true positives and number of true negatives conditional on sensitivity and specificity for each study and constructs a bivariate normal model on the logit transforms of sensitivity and specificity between studies. This model accounts for within- and between-study variability and uses correlation between the studies to adjust an implicit threshold effect. The results, mean logit transforms of sensitivity and specificity, and related standard errors were back transformed and constructed 95% CI. We calculated the diagnostic odds ratio (DOR) based on the estimates of pooled sensitivity and specificity. DOR is a single global measure for diagnostic

Table I. Characteristics of the included studies

Study ID	*Study design*	*Pts*	*DM type*	*Age, years ± SD*	*Male, %*	*Duration of DM, years ± SD*	*Ulcer description (baseline)*	*Follow-up, months*
ABI								
Ballard,[18] 1995	Obs	55	Type 2: 40% Type 1: 60%	67 ± 13	62	—	Nonhealing ulcer: 91%	8
Castronuovo,[7] 1997	Obs	53	—	71 ± 10	62	—	—	—
Chen,[19] 2010	Obs	38	—	69 ± 9	42	13 ± 3	—	12
Edelman,[20] 1997	RCT	64	—	66 ± 6	1	15 ± 9	—	6
Faglia,[21] 1996	Obs	80	—	61 ± 9	70	—	Ulcer Wagner grade: II, 15%; III, 20%; IV, 65%	12
Faglia,[22] 1996	RCT	70	—	63 ± 10	69	18 ± 10	Ulcer Wagner grade: II, 13%; III, 25%; IV, 62%	2
Faglia,[23] 2002	Obs	221	—	70 ± 9	63	20 ± 6	Ulcer Wagner grade: I, 19%; II, 25%; III, 17%; IV, 38%; V, 1%	14
Hamalainen,[24] 1999	RCT	733	Type 2: 54% Type 1: 46%	47 ± 19	—	12 ± 9	—	84
Hanna,[25] 1997	Obs	29	—	62 ± 3	41	—	—	12
Huang,[26] 2005	RCT	28	Type 2: 71% Type 1: 29%	71 ± 6	64	12 ± 8	Texas wound classification: I C, 32%; I D, 32%; II C, 14%; II D, 14%; III C, 0%; III D, 7%	3
Johansen,[27] 2009	RCT	13	Type 2: 85% IDDM: 15%	64	77	18	—	6
Kalani,[28] 1999	Obs	50	—	61 ± 12	75	26 ± 14	—	12
Lee,[29] 1997	Obs	31	—	63 ± 10	50	—	—	—
Londahl,[30] 2011	RCT	75	Type 2: 71% Type 1: 29%	69 ± 10	—	—	Ulcer size (cm^2): 3.1 (1.2-6.4)	12
Nather,[31] 2008	Obs	202	Type 2: 95% Type 1: 5%	60	54	1-48	Gangrene: 32% Infection: 29% Ulcer: 28% Cellulitis: 6% Necrotizing fasciitis: 4% Charcot osteoarthropathy: 2%	—
Prochazka,[32] 2010	Obs	96	—	65 ± 9	81	—	—	4
Redlich,[33] 2011	Obs	28	Type 2	69 ± 8	82	20 ± 10	Critical limb ischemia and severe infrapopliteal peripheral vascular disease	12
Rigatelli,[34] 2011	Obs	220	—	79 ± 16	51	—	—	37
Winkley,[35] 2007	Obs	253	Type 2: 83% Type 1: 17%	62 ± 14	64	13.2	Duration of ulcer: 3.1 ± 3.6 months Ulcer size (cm^2): ≤1, 48.6%; >1, 51.4%	18
Xu,[36] 2011	Obs	37	Type 2: 73% Type 1: 35%	71 ± 9	65	18 ± 6	—	9
$TcPo_2$								
Ay,[37] 2004	Obs	50	—	58 ± 8	66	16 ± 3	—	1
Ballard,[18] 1995	Obs	55	Type 2: 40% Type 1: 60%	67 ± 13	62	—	Nonhealing ulcer: 91%	8
Caselli,[38] 2005	Obs	43	Type 2: 95% Type 1: 5%	73	58	20	Ulcer Wagner grade IV, 100%	11
Ezio,[39] 2010	Obs	261	—	73 ± 9	67	18 ± 12	Ulcer Wagner grade: 0, 6%; I, 30%; II, 10%; III, 7%; IV, 46%	—
Faglia,[21] 1996	Obs	80	—	61 ± 9	70	—	Ulcer Wagner grade: II, 15%; III, 20%; IV, 65%	12
Faglia,[22] 1996	RCT	70	—	63 ± 10	69	18 ± 10	Ulcer Wagner grade: II, 13%; III, 25%; IV, 62%	2
Faglia,[23] 2002	Obs	221	—	70 ± 9	63	20 ± 6	Ulcer Wagner grade: I, 19%; II, 25%; III, 17%; IV, 38%; V, 1%	14
Faglia,[40] 2005	Obs	993	—	70 ± 9	67	18 ± 11	Texas wound classification: 0 C, 12%; I C, 8%; I D,	26

(*Continued on next page*)

Table I. Continued.

Study ID	*Study design*	*Pts*	*DM type*	*Age, years ± SD*	*Male, %*	*Duration of DM, years ± SD*	*Ulcer description (baseline)*	*Follow-up, months*
							7%; II C, 6%; II D, 13%; III C, 3%; III D, 50%	
Faglia,[41] 2007	Obs	564	—	70 ± 10	65	17 ± 11	Ulcer Wagner grade: 0, 16%; I, 15%; II, 14%; III, 10%; IV, 46%	64
Ferraresi,[42] 2009	Obs	101	—	66 ± 9	84	15 ± 5	—	35
Hanna,[25] 1997	Obs	29	—	62 ± 3	41	—	—	12
Ichioka,[43] 2009	Obs	75	—	65	67	—	—	—
Jacqueminet,[44] 2005	Obs	32	Type 2: 84% Type 1: 16%	67 ± 10	85	22 ± 12	—	12
Kalani,[28] 1999	Obs	50	—	61 ± 12	75	26 ± 14	—	12
Khodabandehlou,[45] 2004	Obs	38	Type 2: 71% Type 1: 29%	68 ± 8	—	16 ± 11	—	12
Kim,[46] 2011	Obs	23	—	69 ± 7	74	20 ± 10	Ischemic diabetic ulcer	20
Londahl,[30] 2011	RCT	75	Type 2: 71% Type 1: 29%	69 ± 10	—	—	Ulcer size (cm^2): HBOT, 3.1 (1.2-6.4)	12
Nouvong,[5] 2009	Obs	66	Type 2: 57% Type 1: 43%	52 ± 9	88	13 ± 9	Ulcer size (cm^2): healed, 3.2 ± 3.9; nonhealed, 5.8 ± 6.2	6
Prochazka,[32] 2010	Obs	96	—	65 ± 9	81	—	—	4
Redlich,[33] 2011	Obs	28	Type 2	69 ± 8	82	20 ± 10	Critical limb ischemia and severe infrapopliteal peripheral vascular disease	12
Rigatelli,[34] 2011	Obs	220	—	79 ± 16	51	—	—	37
Uccioli,[47] 2010	Obs	510	Type 2: 93% Type 1: 7%	70 ± 1	64	20 ± 1		20
Wattel,[48] 1990	Obs	11	—	—	—	—	Chronic arterial insufficiency ulcers: 82%	12
Weng,[49] 2009	Obs	61	—	—	—	—	—	—
Zgonis,[50] 2005	Obs	35	Type 2: 97% Type 1: 3%	—	—	—	—	7
SPP								
Castronuovo,[7] 1997	Obs	53	—	71 ± 10	62	—	—	—
Prochazka,[32] 2010	Obs	96	—	65 ± 9	81	—	—	4
TBI								
Kalani,[28] 1999	Obs	50	—	61 ± 12	75	26 ± 14	—	12
Prochazka,[32] 2010	Obs	96	—	65 ± 9	81	—	—	4
TBP								
Kalani,[28] 1999	Obs	50	—	61 ± 12	75	26 ± 14	—	12
Prochazka,[32] 2010	Obs	96	—	65 ± 9	81	—	—	4
APSV								
Bishara,[4] 2009	Obs	62	—	63 ± 6	68	—	—	—
Microvascular Sao_2								
Rajbhandari,[6] 1999	Obs	14	Type 2: 86% Type 1: 14%	67 ± 10	93	14 ± 6	Duration of ulcers: 12 ± 10 weeks	9
Hyperspectral imaging								
Nouvong,[5] 2009	Obs	66	Type 2: 57% Type 1: 43%	52 ± 9	88	13 ± 9	Ulcer size (cm^2): 4.0	6

ABI, Ankle-brachial index; *APSV,* ankle peak systolic velocity; *DM,* diabetes mellitus; *HBOT,* hyperbaric oxygen therapy; *IDDM,* insulin-dependent diabetes mellitus; *Obs,* observational study; *Pts,* patients; *RCT,* randomized controlled trial; *Sao_2,* oxygen saturation; *SD,* standard deviation; *SPP,* skin perfusion pressure; *TBI,* toe-brachial index; *TBP,* toe blood pressure; *$TcPo_2$,* transcutaneous oxygen measurement; *Type 2,* non-insulin-dependent diabetes mellitus.

accuracy, used for general estimation of discriminative power of diagnostic procedures, and helps in comparing two or more diagnostic tests. DOR of a test is the ratio of the odds of positivity in subjects with disease relative to the odds in subjects without disease. We also pooled difference of test score across the included studies and constructed random-effects models using the DerSimonian and Laird method.[14] The effect size, standardized mean difference (SMD), was calculated using Hedges' adjusted g measure.[15] SMD is used when we compare tests that used different units. The results are standardized (ie, expressed in standard deviation units) to allow comparison between tests.

We assessed heterogeneity across individual studies using the I^2 statistic and Cochran Q test. Publication bias was assessed by the Begg adjusted rank correlation test.[16] All statistical analyses were conducted using Stata version 12 (StataCorp, College Station, Tex).

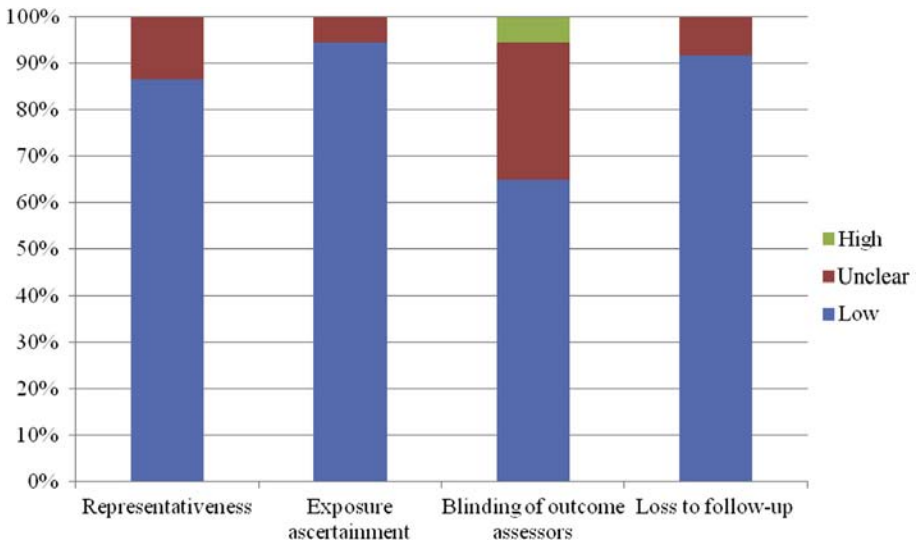

Fig 2. Risk of bias assessment of the included studies. *High risk*: studies do not meet quality criteria. *Unclear*: not enough information to judge study quality. *Low risk*: studies meet quality criteria.

Table II. Pooled sensitivity, specificity, and diagnostic odds ratio (*DOR*) of ankle-brachial index (*ABI*) and transcutaneous oxygen measurement ($TcPo_2$) tests

	ABI		$TcPo_2$	
Outcome	*Estimate*	*95% CI*	*Estimate*	*95% CI*
Complete ulcer healing				
Sensitivity	0.48	0.36-0.61	0.72	0.61-0.81
Specificity	0.52	0.42-0.63	0.86	0.68-0.95
DOR	1.02	0.40-2.65	15.81	3.36-74.45
Limb amputation				
Sensitivity	0.52	0.49-0.54	0.75	0.73-0.77
Specificity	0.73	0.63-0.81	0.58	0.52-0.64
DOR	2.89	1.65-5.05	4.14	2.98-5.76

CI, Confidence interval.

Sensitivity analysis. We constructed multivariate nested random-effects meta-regression models across all included studies to further compare prognostic accuracy of clinical tests.[17] To compare the regression coefficients between different tests in the model, we standardized the coefficients with one standard deviation. Thus, the standardized coefficients represent the standard deviation change of an outcome associated with one standard deviation increase of a test score. The higher value suggests the better discriminant test performance. The sensitivity analysis provided an alternative method to evaluate the findings.

RESULTS

Our searches identified 229 potential studies; 95 were retrieved for full-text screening, and 37 met our inclusion criteria and thus were included in this systematic review (Fig 1). Among them, 32 were observational studies and 5 were randomized controlled trials (RCTs). As the five RCTs were not initiated for evaluating diagnostic tests and were not prognostically balanced between test group and comparison group, we considered them observational studies in this review. The characteristics of the included studies are listed in Table I.

Risk of bias

Fig 2 reports the quality indicators of the included studies. The quality of the included studies was generally adequate. Blinding of outcome assessors was the quality indicator most absent; 13 of the 37 studies did not meet the criterion or did not provide sufficient information for evaluation. Because of the limited number of studies evaluating each test, it was inappropriate to conduct statistical tests to assess publication bias for almost all of the screening tests.[51] The only exception was the $TcPo_2$ test. We found no evidence of publication bias in the outcomes of interest using the Begg adjusted rank correlation test ($P > .05$). In summary, the risk of bias within the studies is medium.

Predictive ability of tests

Meta-analysis was possible on studies of ABI and $TcPo_2$. Because of the limited number of available studies on other tests, we were unable to pool prognostic accuracy of SPP, TBP, TBI, APSV, Sao_2, and hyperspectral imaging.

ABI. Twenty studies evaluated ABI values with a total of 2376 patients (range, 13-733). The patients were observed for an average of 15 months (range, 2-84). The pooled ABI values were significantly higher in the healed ulcer group than in the nonhealed group (SMD, 0.42; 95% CI, 0.05-0.79; $I^2 = 15.7\%$; heterogeneity, $P = .32$). The combined difference between the amputated limb group and the nonamputated group was also significant (SMD, −0.99; 95% CI, −1.44 to −0.54; $I^2 = 44.5\%$; heterogeneity, $P = .13$).

In terms of the ability of the test to predict healing, Table II summarizes the sensitivity, specificity, and DOR of ABI for predicting healed foot ulcers and limb amputations. In general, the prognostic accuracy of using the ABI for predicting healed foot ulcers was low, with the sensitivity of 0.48 (95% CI, 0.36-0.61) and the specificity of 0.52 (95% CI, 0.42-0.63). The overall DOR was 1.02 (95% CI, 0.40-2.64). In predicting limb amputations, the sensitivity was 0.52 (95% CI, 0.49-0.54) with the specificity of 0.73 (95% CI, 0.63-0.81). The DOR was 2.89 (1.65-5.05), suggesting a slightly better test performance for this outcome.

$TcPo_2$. Of the 37 included studies, 25 assessed $TcPo_2$; 3789 patients (range, 11-993) were included in these studies. The average follow-up length was 16 months (range, 1-64). There was a significant difference of $TcPo_2$ values between the healed group and the nonhealed group (SMD, 1.80; 95% CI, 1.06-2.54; $I^2 = 92.3\%$; heterogeneity, $P < .001$). The SMD was −2.26 (95% CI, −4.13 to −0.40) when the amputated-limb group was compared with the nonamputated group ($I^2 = 96.8\%$; heterogeneity, $P < .001$).

In terms of the ability of the test to predict healing (Table II), the results suggested high accuracy of the $TcPo_2$ test for predicting both ulcer healing and limb amputation. For ulcer healing, the combined sensitivity and specificity were 0.72 (95% CI, 0.61-0.81) and 0.86 (95% CI, 0.68-0.95), respectively. The DOR was 15.81 (95% CI, 3.36-74.45). For limb amputations, we found lower but still significantly better DOR with the combined estimate of 4.14 (95% CI, 2.98-5.76).

SPP. Two studies evaluated prognostic performance of the SPP test.[7,32] Castronuovo et al[7] studied a convenience sample of 53 critical limb ischemia patients, 75% of whom had diabetes. Using the threshold of 30 mm Hg, they estimated that the sensitivity for healed ulcers was 85% with the specificity of 73%. The overall area under the receiver operating characteristic curve was 0.79. Prochazka et al[32] compared SPP values between the healed group and the nonhealed group and found a significant difference (111.19 mm Hg vs 68.57 mm Hg, respectively).

TBP. We identified two studies reporting TBP measurements in patients with DFUs.[28,32] Kalani et al[28] estimated that the sensitivity and specificity for TBP were 15% and 97%, respectively, using a cutoff point of 30 mm Hg. The positive predictive value and the negative predictive value were 67% and 77%, respectively. Prochazka et al[32] also found a significant difference on TBP values between the healed group and the nonhealed group (25.63 mm Hg vs 12.43 mm Hg, respectively).

TBI. Two studies evaluated TBI.[28,32] Kalani et al[28] found no significant difference between the healed group and the nonhealed group in terms of TBI measurements. Conversely, Prochazka et al[32] reported that patients with healed wounds had higher TBI mean values at baseline than those who did not eventually heal.

Microvascular Sao_2. One study measured serial microvascular Sao_2 of 21 DFUs at the ulcer margin using a spectrophotometer. In healed ulcers, a significant reduction ($P < .05$) in Sao_2 occurred with healing (Sao_2 dropped from 58% at initial presentation to 45% just before healing). No such changes were noted on the control sites.[6] The study concluded that serial microvascular oxygen measurements may be used to identify at an early stage those ulcers that are unlikely to heal and may require surgical intervention.

APSV. Bishara et al[4] evaluated the performance of APSV. Using a sample of 100 limbs, the APSV value was significantly higher in the healed group than in the nonhealed group (53.0 cm/s vs 19.2 cm/s). The sensitivity, specificity, positive predictive value, and negative predictive value were 92.9%, 90.6%, 92.9%, and 90.6%, respectively. The authors concluded that APSV showed high accuracy in predicting the healing of DFUs.

Hyperspectral imaging. One study tested hyperspectral imaging of tissue oxyhemoglobin and deoxyhemoglobin in 73 DFUs.[5] Nouvong et al estimated that the sensitivity for healing was 80%, the specificity was 74%, and the positive predictive value was 90%.

Comparisons of tests

We were able to pool prognostic performance only for ABI and $TcPo_2$ because of the limited available evidence. As discussed before, $TcPo_2$ more reliably predicted wound healing and limb amputation than ABI. The sensitivity analysis showed $TcPo_2$ with larger standardized coefficients on healed ulcers ($b = 0.311$) and limb amputation ($b = 0.408$) than ABI ($b = 0.287$ and 0.334, respectively), also suggesting a better discriminatory performance of $TcPo_2$ than ABI.

DISCUSSION

Main findings. We conducted a systematic review and meta-analysis to evaluate several available tests to predict wound healing in the setting of DFU and compared the prognostic accuracy of the tests. Eight tests, reported by 37 studies, were included in this study: ABI, APSV, $TcPo_2$, TBI, TBP, microvascular Sao_2, SPP, and hyperspectral imaging.

We found that ABI had poor performance in predicting the healing of foot ulcers and modest performance in predicting limb amputations. $TcPo_2$ was a better test for predicting both outcomes.

With the limited number of the available studies, we were not able to quantitatively compare the prognostic accuracy of APSV, TBI, TBP, Sao_2, SPP, and hyperspectral imaging. Our results are consistent with findings in other studies. A case-controlled study by Reiber et al[52] showed transcutaneous oximetry to be the most associated with the risk of amputation in patients with DFU (compared with ankle-arm blood pressure index <0.45, absence of lower leg vibratory perception, and low levels of high-density lipoprotein subfraction 3).

Our results in the DFU setting are consistent with a systematic review that evaluated transcutaneous oximetry to predict complications of chronic wound healing. It concluded that a periwound level below a cutoff of

20 mm Hg or 30 mm Hg was an independent predictor of chronic wound healing complications (odds ratio, 3.21; 95% CI, 1.07-9.69; $I^2 = 77\%$).[8]

Strengths and limitations. The strengths of this systematic review include a comprehensive literature search, bias protection methods (reviewing and appraising evidence in duplicates), and both qualitative and quantitative summaries of the evidence. A sensitivity analysis was conducted to provide additional support for the findings.

There are several limitations to our findings. First, 32 of the 37 included studies were observational ones. The five RCTs were not designed for assessing test performance; thus, the test and comparison groups were not balanced. All 37 studies are subject to high risk of bias due to baseline imbalance and potential outcome confounding. Second, ecologic bias may affect our conclusions (ie, the performance of different tests was compared across different studies, not within the same study). Third, various and arbitrary choices of threshold may exaggerate test performance.

Thus, using the GRADE framework, the overall quality of this evidence (ie, confidence in the estimates) is low.[10,11]

Implications for practice and research. Although we identified some evidence suggesting that $TcPo_2$ has better prognostic accuracy than ABI in predicting wound healing of DFUs, each test has its own limitations in selected patients. ABI is not accurate when patients present with arterial wall calcification (medial calcinosis); TBI cannot be used to measure a toe when it is affected by ulcers or gangrene or has been amputated; SPP requires a cuff inflation to occlude capillary flow, which may be too painful for some patients and is not widely available. Such limitations along with cost, availability, and training factors need to be considered.

CONCLUSIONS

Several tests may predict wound healing in the DFU setting; however, most of the available evidence evaluates only $TcPo_2$ and ABI. The overall quality of the evidence is low, and further research is needed to provide higher quality comparative effectiveness evidence.

AUTHOR CONTRIBUTIONS

Conception and design: ZW, RH, BF, TE, AT, LP, JM, MM
Analysis and interpretation: ZW, MM
Data collection: ZW, RH, BF, TE, AT, LP, MM
Writing the article: ZW, LP, JM, MM
Critical revision of the article: ZW, RH, BF, TE, AT, LP, JM, MM
Final approval of the article: ZW, RH, BF, TE, AT, LP, JM, MM
Statistical analysis: ZW, MM
Obtained funding: MM
Overall responsibility: MM

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Submitted Sep 8, 2015; accepted Oct 8, 2015.

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APPENDIX (online only).

Data sources and search strategies

A comprehensive search of several databases from each database's earliest inclusive dates to October 2011 (any language, any population) was conducted. The databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid Embase, Ovid Cochrane Database of Systematic Reviews, Ovid Cochrane Central Register of Controlled Trials, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principle investigator. Controlled vocabulary supplemented with keywords was used to search for the topic: tests for prediction of diabetic foot wound healing, limited to randomized and nonrandomized studies.

Actual search strategy

Ovid. Databases: Embase 1988 to 2011 Week 40, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present, EBM Reviews—Cochrane Central Register of Controlled Trials 4th Quarter 2011, EBM Reviews—Cochrane Database of Systematic Reviews 2005 to October 2011.

Search strategy:

#	*Searches*	*Results*
1	((diabetic or diabetes) adj3 (foot or feet)).mp.	14923
2	exp Diabetic Foot/	11805
3	1 or 2	14923
4	exp Ankle Brachial Index/	3560
5	((ankle or toe) adj brachial adj2 (index or indices or ratio)).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	7603
6	4 or 5	7603
7	exp transcutaneous oxygen monitoring/	1655
8	exp Blood Gas Monitoring, Transcutaneous/	3814
9	"transcutaneous partial pressure of oxygen".mp.	111
10	tcpo2.mp.	1665
11	hyperspectral imag*.mp.	635
12	skin perfusion pressure*.mp.	146
13	or/4-12	12855
14	3 and 13	417
15	exp controlled study/	3639965
16	exp evidence based medicine/	518676
17	evidence-based.mp.	175991
18	((control$ or randomized) adj2 (study or studies or trial or trials)).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	4669099
19	meta analysis/	87758
20	meta-analys$.mp.	139569
21	exp "systematic review"/	44105
22	systematic review$.mp.	98690
23	exp Guideline/ or exp Practice Guideline/	271941
24	guideline$.ti.	87215
25	or/15-24	5188997
26	exp case study/	1572995
27	exp Cohort Studies/	1330764
28	exp longitudinal study/	880349
29	exp retrospective study/	628418
30	exp prospective study/	532053
31	exp observational study/	23108
32	exp comparative study/	2198791
33	exp clinical trial/	1477518
34	exp evaluation/	1088304
35	exp twins/	39276
36	exp validation study/	28010
37	exp experimental study/ or exp field study/ or exp in vivo study/ or exp panel study/ or exp pilot study/ or exp prevention study/ or exp quasi experimental study/ or exp replication study/ or exp theoretical study/ or exp trend study/	6878167
38	((clinical or evaluation or twin or validation or experimental or field or "in vivo" or panel or pilot or prevention or replication or theoretical or trend or comparative or cohort or longitudinal or retrospective or prospective or population or concurrent or incidence or follow-up or observational) adj (study or studies or survey or surveys or analysis or analyses or trial or trials)).mp.	6826285
39	("case study" or "case series" or "clinical series" or "case studies").mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	154865

(*Continued on next page*)

Continued.

#	*Searches*	*Results*
40	or/26-39	12888282
41	14 and (25 or 40)	307
42	14	417
43	limit 42 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or twin study) [Limit not valid in Embase,CDSR; records were retained]	106
44	41 or 43	311
45	limit 44 to (book or book series or editorial or erratum or letter or note or addresses or autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	7
46	44 not 45	304
47	from 14 keep 404-417	14
48	46 or 47	305
49	remove duplicates from 48	221

Scopus.

1 TITLE-ABS-KEY((diabetes w/3 foot) or (diabetic w/3 foot) or (diabetes w/3 feet) or (diabetic w/3 feet))
2 TITLE-ABS-KEY((ankle w/1 brachial w/2 index) or (ankle w/1 brachial w/2 indicies) or (ankle w/1 brachial w/2 ratio) or (toe w/1 brachial w/2 index) or (toe w/1 brachial w/2 indicies) or (toe w/1 brachial w/2 ratio) or "transcutaneous partial pressure of oxygen" or ("transcutaneous oxygen" w/3 monitor*) or tcpo2 or "hyperspectral imag*" or "skin perfusion pressure*")
3 TITLE-ABS-KEY((evidence W/1 based) OR (meta W/1 analys*) OR (systematic* W/2 review*) OR guideline OR (control* W/2 stud*) OR (control* W/2 trial*) OR (randomized W/2 stud*) OR (randomized W/2 trial*))
4 TITLE-ABS-KEY("comparative study" OR "comparative survey" OR "comparative analysis" OR "cohort study" OR "cohort survey" OR "cohort analysis" OR "longitudinal study" OR "longitudinal survey" OR "longitudinal analysis" OR "retrospective study" OR "retrospective survey" or "retrospective analysis" OR "prospective study" OR "prospective survey" OR "prospective analysis" OR "population study" OR "population survey" OR "population analysis" OR "concurrent study" OR "concurrent survey" OR "concurrent analysis" or "incidence study" OR "incidence survey" OR "incidence analysis" OR "follow-up study" OR "follow-up survey" OR "follow-up analysis" or "observational study" OR "observational survey" OR "observational analysis" OR "case study" OR "case series" OR "clinical series" OR "case studies" or "clinical study" OR "clinical trial" or "evaluation study" OR "evaluation survey" OR "evaluation analysis" or "twin study" OR "twin survey" OR "twin analysis" or "validation study" OR "validation survey" OR "validation analysis" or "experimental study" OR "experimental analysis" or "field study" OR "field survey" OR "field analysis" or "in vivo study" OR "in vivo analysis" or "panel study" OR "panel survey" OR "panel analysis" or "pilot study" OR "pilot survey" OR "pilot analysis" or "prevention study" OR "prevention survey" OR "prevention analysis" or "replication study" OR "replication analysis" or "theoretical study" OR "theoretical analysis" or "trend study" OR "trend survey" OR "trend analysis")
5 1 and 2 and (3 or 4)
6 PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
7 5 and not 6
8 DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
9 7 and not 8

A systematic review and meta-analysis of débridement methods for chronic diabetic foot ulcers

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Background: **Several methods of débridement of diabetic foot ulcers are currently used. The relative efficacy of these methods is not well established.**

Methods: **This systematic review and meta-analysis was conducted to find the best available evidence for the effect of débridement on diabetic foot wound outcomes. We searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and Scopus through October 2011 for randomized controlled studies (RCTs) and observational comparative studies.**

Results: **We identified 11 RCTs and three nonrandomized studies reporting on 800 patients. The risk of bias was moderate overall. Meta-analysis of three RCTs showed that autolytic débridement significantly increased the healing rate (relative risk [RR], 1.89; 95% confidence interval [CI] 1.35-2.64). Meta-analysis of four studies (one RCT) showed that larval débridement reduced amputation (RR, 0.43; 95% CI, 0.21-0.88) but did not increase complete healing (RR, 1.27; 95% CI, 0.84-1.91). Surgical débridement was associated with shorter healing time compared with conventional wound care (one RCT). Insufficient evidence was found for comparisons between autolytic and larval débridement (one RCT), between ultrasound-guided and surgical débridement, and between hydrosurgical and surgical débridement.**

Conclusions: **The available literature supports the efficacy of several débridement methods, including surgical, autolytic, and larval débridement. Comparative effectiveness evidence between these methods and supportive evidence for other methods is of low quality due to methodologic limitations and imprecision. Hence, the choice of débridement method at the present time should be based on the available expertise, patient preferences, the clinical context and cost. (J Vasc Surg 2016;63:37S-45S.)**

Chronic foot ulcers are frequent complications in patients with diabetes that lead to high hospitalization and amputation rates.[1] Approximately 15% of patients with diabetes will suffer foot ulcer at some point in their lives. Among them, 14% to 24% will require an amputation, making the foot ulcer the main predictor of future amputation.[2]

Débridement is generally defined as "the process in which all materials incompatible with healing are removed from a wound."[3] Several methods are currently used for débridement, including surgery, conventional dressing, larvae, enzyme preparation, polysaccharide beads, and hydrogels.[4] The best method among these is yet to be determined. Therefore, the Society for Vascular Surgery commissioned this evidence synthesis report to evaluate the quality of the evidence supporting the existing methods of débridement and estimate the magnitude of benefit and relative efficacy.

METHODS

This systematic review is protocol-driven and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[5]

Eligibility criteria. Eligible studies were randomized trials (RCTs) and controlled observational studies that enrolled patients with diabetic foot ulcers treated by any method of débridement and compared with any different method and reported the outcomes of interest. We were interested in studies that assess the effect of the intervention on patient-important outcomes,[6] such as complete wound healing, time to complete wound healing, amputation,

From the Evidence-based Practice Center,[a] Mayo Clinic Libraries,[f] and Division of Preventive, Occupational and Aerospace Medicine,[g] Mayo Clinic, Rochester; the Unidad de Conocimiento y Evidencia, Universidad Peruana Cayetano Heredia, Lima[b]; the Second Medical Department, Aristotle University, Thessaloniki[c]; the Department of Podiatry, Phoenix VA Health Care System, Phoenix[d]; and the Department of Internal Medicine, University of Missouri, Columbia.[e]

This review was partially funded by a contract from the Society for Vascular Surgery, which had no involvement in the study design; collection, analysis, and interpretation of data; manuscript writing; or the decision to submit the manuscript for publication.

Author conflict of interest: none.

Additional material for this article may be found online at www.jvascsurg.org.

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Independent peer review and oversight was provided by members of the Society for Vascular Surgery Document Oversight Committee: Peter Gloviczki, MD (Chair), Martin Bjorck, MD, Ruth Bush, MD, Thomas Forbes, MD, Michel Makaroun, MD, and Gregory Moneta, MD.

0741-5214

http://dx.doi.org/10.1016/j.jvs.2015.10.002

infection, and relapse rates. Studies were included regardless of language, size, or duration of patient follow-up. We excluded articles that were not original studies, such as review articles, commentaries, and letters, and also excluded uncontrolled studies.

Study identification. An expert reference librarian (L.P.) designed and conducted the electronic search strategy with input from a study investigator with expertise in conducting systematic reviews (M.H.M.). We searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and Scopus through October 2011. We identified additional candidate studies by review of the bibliographies of included articles and contact with experts. Controlled vocabulary supplemented with keywords was used to search for the topic of diabetic foot débridement, limited to randomized and nonrandomized studies. The detailed search strategy is available in the Appendix (online only).

Data collection. All relevant abstracts were downloaded into an endnote library and uploaded into an online reference management system (DistillerSR; Evidence Partners, Ottawa, ON, Canada). Reviewers working independently and in duplicate screened the abstracts for eligibility. Disagreements were automatically upgraded to the next level of screening. Full text of eligible abstracts were retrieved and screened in duplicate. Disagreements at this level were resolved by discussion and consensus. We calculated the inter-reviewer agreement beyond chance (κ) during the full-text screening level.

Data were extracted in duplicate using a standardized, piloted, Web-based form. For each study we abstracted a detailed description of baseline characteristics (main demographic characteristics, type and duration of diabetes, size, and duration of the ulcer, etc) and interventions received (active or control) for all participants enrolled. We also collected the quality assessment and outcome data. A third reviewer compared the reviewers' data and resolved inconsistencies by referring to the full-text article.

Methodologic quality assessment. Two reviewers independently assessed the quality of studies included. Nonrandomized studies were evaluated using the Newcastle-Ottawa scale.[7] We assessed outcome ascertainment, adjustment for confounders, proportion of patients lost to follow-up, and sample selection in each study. RCTs were evaluated using the Cochrane risk of bias assessment tool.[8] We assessed randomization, blinding, allocation concealment, baseline imbalances (ie, differences between the study arms within individual studies in distribution of prognostic factors), follow-up data, and bias due to funding. The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods.[9,10] Following this approach, randomized trials are considered to warrant high quality of evidence (ie, high certainty) and observational studies warrant low quality of evidence. The evidence grading can then be increased if a large effect is observed or decreased if other factors are noted such as studies being at increased risk of bias or imprecise (small with wide confidence intervals).

Statistical analysis. We pooled the relative risk (RR) and 95% confidence interval (CI) across included studies using random-effect meta-analysis described by DerSimonian and Laird.[11] Between-studies heterogeneity was calculated by the I^2 statistic, which estimates the proportion of variation in results across studies that is not due to chance.[12] Meta-analysis was completed using Comprehensive Meta-analysis (CMA) 2.2 software (Biostat Inc, Englewood, NJ).

Subgroup analysis and publication bias. We did not perform subgroup analyses because of the limited number of studies that compared each intervention. Evaluation of publication bias was not feasible due to the small number of included studies.[13]

RESULTS

Search results and included studies. The literature search yielded 692 potentially relevant abstracts. Thirteen studies fulfilled our inclusion criteria and were eligible for data extraction, of which six reported sufficient data for a meta-analysis (Fig 1). We identified 14 interventional studies (11 RCTs and three controlled cohorts), including data from 800 patients with foot ulcers undergoing débridement with surgical, autolytic, larval, or ultrasound-assisted approaches. The characteristics of the included studies are described in Table I, and details of the intervention methods are described in Table II. The adjusted agreement between reviewers (κ) averaged 0.94, as calculated by the online system.

Methodologic quality and risk of bias. The quality of the included studies ranged from fair to moderate. Randomization and allocation concealment were adequately described only in four and two of 11 RCTs, respectively. Patients and caregivers were blinded only in three studies. Lack of blinding is less of a concern for objective outcomes, such as amputation, but can introduce a significant bias for subjective or assessor-dependent outcomes such as wound healing. No baseline imbalances were mentioned in 60% of the studies, and almost half of the trials did not report loss of follow-up data. Overall quality of observational studies was moderate. The samples were representative in two studies; however, groups were comparable in all three of the studies. Moreover, follow-up was adequate, and all studies reported a 100% response rate. Nevertheless, none of them adjusted for potential confounders. Tables III and IV describe the quality of included studies.

Meta-analysis. Based on three RCTs, autolytic débridement was associated with a statistically significant increase in healing rates compared with standard wound débridement by gauze and conventional wound care (RR, 1.89; 95% CI, 1.35-2.64; $P < .001$), $I^2 = 0.00\%$ (Fig 2). Autolytic débridement is applied by using hydrogel type dressings that promote a moist environment to enhance the function of naturally occurring enzymes and facilitate shedding of devitalized tissue.

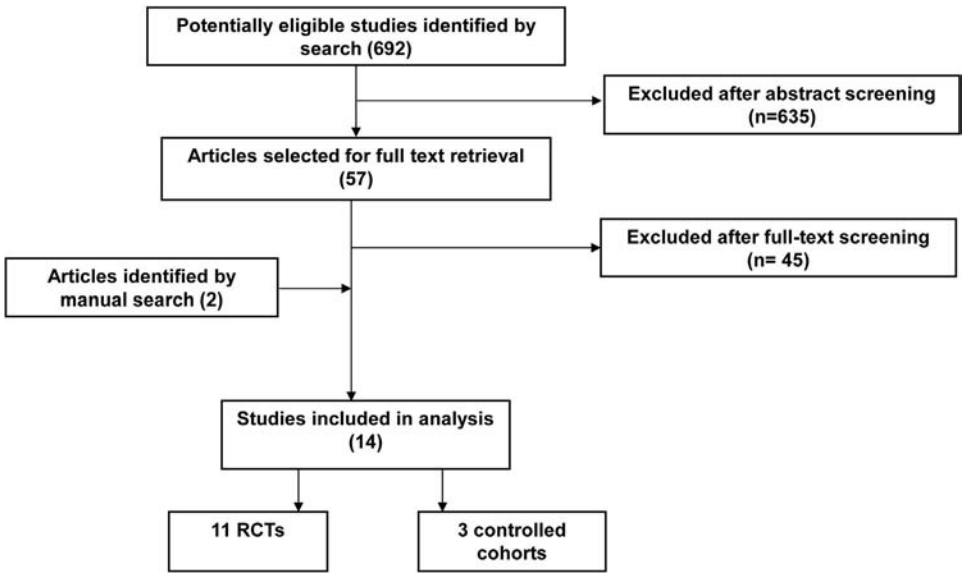

Fig 1. The process of study selection. *RCT,* Randomized controlled trial.

A meta-analysis of three comparative studies showed no significant difference in complete healing rates between larval débridement and conventional wound care (RR, 1.27; 95% CI, 0.84-1.91; $P = .37$), $I^2 = 34\%$. However, two of the studies also reported a significant reduction in the rate of amputation in favor of larval therapy (RR, 0.43; 95% CI, 0.21-0.88; $P = .02$), $I^2 = 0\%$ (Fig 3). Larval therapy (also called therapeutic myiasis) is done using the larvae of the greenbottle fly (*Lucilia sericata*), which naturally feed on dead tissue, cellular debris, and serous drainage. Larval therapy is provided using a prefabricated foam or as free-range loose larvae applied directly to the wound and retained in place by a dressing.

One RCT[14] compared maggot-based débridement vs autolytic débridement with hydrogel and reported a significant difference in number of patients who achieved >50% reduction of the wound area after 10 days in favor of maggot therapy (51.1% vs 27.1%; RR, 1.89; 95% CI, 1.21-2.96; $P = .005$). However, the two interventions did not differ significantly in the number of patients who achieved complete wound healing (RR, 2.5; 95% CI, 0.50-12.46; $P = .26$).

One RCT[15] compared surgical débridement vs conventional wound dressing and reported a healing rate of 95% (21 of 22 ulcers) in the surgical group vs 79.2% (19 of 24 ulcers) in the conventional group; however, the association was not statistically significant (RR, 1.2; 95% CI, 0.96-1.51; $P = .10$). The healing time was significantly shorter in the surgical group than in the conventional group (46.73 ± 38.94 vs 128.9 ± 86.60 days; $P < .001$). Infective complications occurred less often in the first group (1 of 22 [4.5%] vs 3 of 24 [12.5%]; RR, 0.36; 95% CI, 0.04-3.24; $P = .36$) as did relapses of ulcerations (3 vs 8; RR, 0.41; 95% CI, 0.12-1.35; $P = .14$); nevertheless, neither outcome reached statistical significance.

Ultrasound débridement was compared with surgical débridement in two small RCTs published as a thesis.[16,17] Low-frequency ultrasound is applied with a wound-treatment solution through the probe tip in a noncontact fashion. Both studies reported significantly smaller-sized wounds in the ultrasound group after 2 to 5 weeks. Data on complete wound healing were not available. The quality of evidence was downgraded due to indirectness of outcome and inadequate follow-up time.

In one RCT,[18] a hydrosurgical débridement system—a device that concurrently cuts and aspirates soft tissue—was compared with a surgical débridement and reported similar clinical efficacy for the median time to complete wound healing (71 days in the hydrosurgical group vs 74 days in the surgical group; $P = .733$). The quality of the evidence was downgraded due to indirectness and high risk of bias.

One RCT[19] assessing the use of superoxidized aqueous solution vs saline for lavage in a hydrosurgical débridement system reported no significant change in wound size at week 4 ($P = .4$). The quality of evidence was low due to methodologic limitations of the study.

Another study[20] compared adhesive zinc oxide tape vs occlusive hydrocolloid dressing and reported a significant difference in complete disappearance or at least 50% reduction in the necrotic area in favor of adhesive zinc oxide (RR, 2.33; 95% CI, 1.11-4.89; $P = .02$) The quality of evidence was low due to methodologic limitations and imprecision.

Finally, one study published in abstract form[21] compared two types of hydrogels used for autolytic débridement and reported that complete wound healing was achieved in 35% of patients in one group compared with 19% in the second group. The wounds reduced in

Table I. Characteristics of the included studies

Study name	*Country*	*Care setting*	*DM type and duration, HbA_{1c}, ulcer duration, comorbidities*	*Patients, No.*	*Follow-up, months*	*Age, Mean years*	*Male, %*	*Ulceration area, cm^2*
Apelqvist,[20] 1990	Sweden	Outpatients with combined foot care team	Mean DM duration, 20 years; HbA_{1c}, 8.2; ulcer duration, 1-105 weeks	44	1.25	63	59	2.2
Armstrong,[22] 2005	USA	Large referral-based diabetic foot clinic	DM duration, 15.5 years	60	≥6	72	86.7	All: 12.1 ± 5.7; MDT: 11.8 ± 4.5; control: 12.4 ± 6.7
Bowling,[19] 2011	USA	Hospital and community patients	Type 1 or type 2 DM, chronic ulcers >4 weeks	20	1	54	60	All: 2.4; super oxidized group: 3.0 ± 3.7, saline group: 1.8 ± 1.7
Caputo,[18] 2008	USA	Community hospital (Clara Maass Medical Center)	NR	41	3	68	63.4	(Median) All: 4.3; Versajet: 5.9; conventional: 3.9
D'Hemecourt,[28] 1998	USA	Multicenter (10 sites)	Type 1 or type 2 DM	172	Up to 5	19 years or older	74	NaCMC gel: 3.2; good wound care: 3.5
Jensen,[29] 1998	USA	Outpatient setting	NR	31	Up to 4-5	NR	NR	NR
Markevich,[14] 2000	Europe	Multicenter study	DM duration, 16 years, with neuropathic wounds that required débridement	140	30	54	NR	MDT: 14.9; hydrogel: 15.1
Paul,[23] 2009	Malaysia	General hospital orthopedics service	NR	59	NR	56	64.4	NR
Piaggesi,[15] 1998	Italy	Hospital department foot clinic	Type 1 or 2 DM; mean HbA_{1c}, 9.2%, DM for 17 years, with clinical neuropathy and ulcer >3 weeks	41	6 (up to 11 in some patients)	64	NR	NR
Sherman,[24] 2003	USA	Maggot therapy service, Department of Pathology, University of California Irvine	Ulcer duration >2 weeks; most had peripheral venous or arterial disease	18 (20 ulcers)	>2	67	NR	All: 9.8 cm^2; conventional therapy: 6.3; MDT: 13.5
Singh,[16] 2006	Malaysia	University of Malaya Medical Centre	Type 1 DM: 8.5%; type 2 DM: 91.5%.	59 (60 ulcers)	0.5	57	55	NR
Vandeputte,[30] 1996	Belgium	Wound-care department	NR	29	NR	NR	NR	NR
Whalley,[21] 2001	UK	Probably secondary care setting	NR	74 (66 evaluated)	2.5 or until healing	NR	NR	Purilon: 2.5; IntraSite: 2.4
Yao,[17] 2014	USA	Probably secondary care setting	83% type 2 DM; ulcer duration: 36.4 ± 24.8 weeks	12	5 weeks	40-72	66	1.9, 2.1, and 2.5, for the 3 groups

DM, Diabetes mellitus; *HbA_{1c},* glycated hemoglobin; *NaCMC,* sodium carboxymethylcellulose; *MDT,* maggot débridement therapy; *NR,* not reported; *UK,* United Kingdom; *USA,* United States of America.

Table II. Inclusion criteria and interventions in each study

Study	*Inclusion criteria*	*Exclusion criteria*	*Intervention 1*	*Intervention 2*
Apelqvist,[20] 1990	Diabetic patients with superficial full-thickness skin ulcer below the ankle, systolic toe pressure >45 mm Hg or absence of cutaneous erythema; only the largest in every patient	Clinical signs of cellulitis, positive patch test, inappropriate application of dressing	Adhesive zinc oxide tape	Occlusive hydrocolloid dressing (DuoDerm)
Armstrong,[22] 2005	Diabetic patients with single DFU, inability to walk without the use of a wheel chair or other device, diagnosis of peripheral vascular disease without surgical intervention, >6 months of follow-up information	No clinically vascular disease; not grade C or D of University of Texas grading scale	Maggot débridement	Standard wound care
Bowling,[19] 2011	Hospital and community adult patients with type 1 and type 2 DM who had chronic (>4 weeks) nonclinically infected DFUs where necrotic tissue was present and mechanical débridement was indicated	Ulcers >25 cm^2, grade 3 (University of Texas classification), osteomyelitis, peripheral arterial disease (absent pulses, ABI <0.8), use of anticoagulants, immunosuppressive drug treatment, known allergies to chlorine, clinically infected wounds	Superoxidized aqueous solution	Saline solution
Caputo,[18] 2008	Patients with lower extremity ulcers	Not reported	Hydrosurgical débridement	Conventional surgical débridement
D'Hemecourt,[28] 1998[a]	Age ≥19 years, type 1 or type 2 DM, ≥1 full-thickness ulcer (stage 3 or 4), ulcer present 8 weeks before study, 1 cm^2-10 cm^2 postdébridement, $TcPo_2$ >30 mm Hg, chronic diabetic ulcer of lower extremity	Osteomyelitis, outside 1 cm^2-10 cm^2 range, patient had >3 ulcers, cause of ulcer was not diabetic (eg, electrical, chemical or radiation), patients with cancer, concomitant medication to affect wound healing, women who were pregnant, nursing, or of child-bearing potential	Good wound care and NaCMC hydrogel	Good wound care consisted of daily dressing changes, sharp débridement of the ulcer when deemed necessary by the investigator, systemic control of infection if present, and off-loading of pressure
Jensen,[29] 1998	Diabetic patients with an ulcer >1 cm diameter, no infection of ulcer or periwound tissue, Wagner grade 2 ulcer not involving tendon, joint, or bone, documented blood supply consistent with the ability to heal (palpable pulses, noninvasive vascular study), willingness to comply with protocol	Not reported	Carrasyn hydrogel wound dressing (initially treated with sharp débridement, patients received custom-made healing sandals for pressure redistribution)	Wet-to-moist saline gauze (initially treated with sharp débridement, patients received custom-made healing sandals for pressure redistribution)
Markevich,[14] 2000	Patients with DM, mean age 54, mean DM duration 16 years with neuropathic foot wounds	Not reported	Maggot (green-bottle fly)	Hydrogel
Paul,[23] 2009	All patients aged 35-70 years, who were admitted for infected diabetic foot wounds (below ankle) to the orthopedics wards requiring repeat débridement or nonurgent primary débridement	Gangrenous wounds, necrotizing fasciitis, abscesses, wounds with exposed viable bones/viable tendons, wounds that were profusely bleeding, ischemic wounds ABSI <0.75); patients who had entomophobia	Maggot therapy	Conventional therapy (surgical débridement and dressing)
Piaggesi,[15] 1998	New patients with painless ulcer(s) lasting ≥3 weeks, nonischemic, uncomplicated neuropathic ulcers with clinical characteristics of neuropathy; type 1 or 2 DM of at least 5 years' duration	Symptomatic claudication or absence of foot pulses, recent ketoacidosis, renal failure, infection (perilesional edema and erythema, or pus, systemic symptoms, such as fever or leukocytosis, positive wound	Surgical excision of the ulcer (débridement or removal of bone segments underlying the lesion,	Nonoperative treatment (initial débridement and medication of ulcer, relief of weight-bearing,

(*Continued on next page*)

Table II. Continued.

Study	*Inclusion criteria*	*Exclusion criteria*	*Intervention 1*	*Intervention 2*
		swab) congenital foot deformities or diabetic neuroarthropathy, BMI >30 kg/m^2, clinical history of stroke, cardiac failure, cancer, HIV positivity, history of mental illness, subclinical macroangiopathy (ABPI <0.9), osteomyelitis or doubtful cases for osteomyelitis	necessary, subsequent suture of the skin, and relief of weight-bearing for 4 weeks)	regular dressings, and follow-up)
Sherman,[24] 2003	Nonhealing wounds, have contours that could be measured by planimetry, making them eligible for this study	Patients with osteomyelitis or rapidly advancing soft-tissue infection	Maggot therapy (*Phaenicia* or *Lucilia sericata*)	Standard therapy (dry gauze or saline gauze)
Singh,[16] 2006	Type 1 or type 2 DM, with DFUs (grade 0, 1 or 2), sensate feet (based on Neuropathic Disability Score), and at least 1 (dorsalis pedis or posterior tibial) pulses palpable	DFUs grade 3 or 4, patients whose ulcers were covered with a hard scab, patients with peripheral neuropathy based on modified Neuropathic Disability Score, those who did not have at least 1 of the foot pulses palpable (dorsalis pedis artery or posterior tibialis artery)	Ultrasound-assisted wound débridement	Sharp débridement
Vandeputte,[30] 1996	Diabetic patients with a wound (neuropathic or not); whether necrotic or infected wounds	Patients under a systemic antibiotic regimen	Hydrogel dressing	Dry gauze
Whalley,[21] 2001	Neuropathic uncomplicated DFUs (grade 1-2)	Not reported	Purilon gel	IntraSite gel
Yao,[17] 2014	Chronic nonhealing DFUs	Not reported	Noncontact low-frequency ultrasound therapy	Débridement, offloading and moist wound care

ABI, Ankle-brachial index; *ABPI,* ankle-brachial pressure index; *ABSI,* ankle-brachial systolic index; *BMI,* body mass index; *DFU,* diabetic foot ulcers; *DM,* diabetes mellitus; *$TcPo_2$,* transcutaneous oxygen pressure.

[a]The study had 3 arms; the third group (34 patients) was randomized to good wound care and becaplermin. Outcomes for this group were not available.

size from (mean ± standard deviation) 2.5 ± 3.2 cm^2 to 0.6 ± 1.1 cm^2 in the first group and from 2.4 ± 2.9 cm^2 to 1.0 ± 1.8 cm^2 in the second group (the total number of patients was 66, and no statistical testing for significance was reported).

DISCUSSION

We conducted a systematic review and meta-analyses to evaluate the comparative effectiveness of different débridement methods for diabetic foot ulcers. We found low to moderate quality evidence supporting benefits of autolytic débridement with hydrogel and surgical débridement, delivered with ultrasound assistance or other methods. The RCT that compared larva vs autolytic débridement reported a significant reduction in the wound size area in favor of larval therapy, but the number of completely healed ulcers between the groups was similar. When different hydrogels were compared in one RCT, no significant differences were found. Pooling of three controlled cohorts showed that there is no significant difference in the healing rate between larval débridement and conventional wound care but potentially a difference in the amputation rate.[22-24] Overall, the number of included studies and number of events were quite low, making the available evidence imprecise and inconclusive. In addition, the comparison (control) group in the included studies received conventional wound care, the details of which were not well reported and likely varied across studies, particularly in dressing type, débridement type, frequency and intensity, and follow-up frequency.

Our results are consistent with other evidence syntheses attempts. Tian et al[25] conducted a systematic review and meta-analysis and reported that maggot débridement therapy was superior to the control group in diabetic foot ulcers to achieve full healing (RR, 1.8; 95% CI, 1.07-3.02), amputation rate (RR, 0.41; 95% CI, 0.20-0.85), time to healing (RR, −3.70, 95% CI, −5.76 to −0.64), and number of antibiotic-free days (126.8 ± 30.3 days vs 81.9 ± 42.1 days; $P = .001$); however, no significant change was noted in the incidence of infection after intervention (RR, 0.82; 95% CI, 0.65-1.04).[25]

Another systematic review did not find strong evidence to support a specific method of débridement due to sparse data and methodologic limitations of the studies; hence, they did not perform a meta-analysis.[26] A systematic review by the Cochrane collaboration included only RCTs and reported similar conclusions.[4] The present systematic review

Table III. Methodologic quality of randomized trials

Study name	*How was the randomization done?*	*Allocation concealment*	*Blinding*	*Baseline imbalances.*	*Efficient follow-up*	*Adhere to treatment*	*Patients lost to follow-up, %*	*Funding*
Apelqvist,[20] 1990	NR	NR	NR	More men in DuoDerm group	Weekly multidisciplinary meetings	NR	NR	NR
Bowling,[19] 2011	Computer-generated block randomization	Yes; sealed envelopes	Patients, caregivers	No	Yes; weekly visits	Yes	0	Includes for-profit sources
Caputo,[18] 2008	NR	Yes; method not mentioned	NR	No	NR	NR	NR	NR
D'Hemecourt,[28] 1998	Unclear (patients were randomly assigned in a 2:2:1 ratio to 1 of 3 treatment groups)	NR	Yes; patients, care givers and outcome assessors	Yes; group size and ulcer characteristics (mean area, depth, and duration)	NR	NR	0	NR
Jensen,[29] 1998	NR	NR	NR	Ulcer duration longer in Carrasyn group	Yes; weekly visits	NR	16	Includes for-profit sources
Markevich,[14] 2000 (abstract)	NR	NR	Double-blinded	Baseline surface area bigger in hydrogel group	NR	NR	NR	NR
Piaggesi,[15] 1998	Table of randomization	NR	NR	No	Yes; regular visits	Yes	NR	NR
Singh,[16] 2006	Drawing lots	NR	NR	No	NR	NR		NR
Vandeputte,[30] 1996 (abstract)	Preprepared randomization listing	NR	NR	No	NR	NR	NR	NR
Whalley,[21] 2001	NR	NR	NR	No	Yes; regular visits	NR	NR	NR
Yao,[17] 2014	Block randomization	NR	NR	No	Yes; regular visits	NR	0	NR

NR, Not reported.

Table IV. Methodologic quality of cohort studies

Study name	*Sample representativeness*	*Are the 2 groups from the same population?*	*Was the exposure properly verified?*	*Adjustment for confounders*	*Outcome assessment between the 2 groups*	*Adequacy of follow-up*	*Response rate, %*	*Source of study funding?*
Armstrong,[22] 2005	Yes	Yes	Yes	No	Yes, quite similar	Yes	100	NR/unclear
Paul,[23] 2009	Yes	Yes	Yes	No	Yes, quite similar	Yes	100	NR/unclear
Sherman,[24] 2003	Unclear	Yes	Yes	No	Yes, quite similar	Yes	100	Not-for-profit source

expands on the previous findings and brings the evidence base up to date regarding RCTs and observational studies that evaluated all types of débridement.

Clinical and practice implications. The available evidence points toward putative benefits of autolytic, larval, and surgical débridement. However, our confidence in the difference between treatments is rather low and may change as future research accumulate. Therefore, the choice of débridement therapy remains a decision to be made based on patient preferences, clinical context, availability of surgical expertise and materials, and cost. A cost-effectiveness analysis highlighted the uncertainty about cost-effectiveness that likely differ based on analysis assumptions and the environment of care delivery.[27] The accompanying guideline by the Society for Vascular Surgery will demonstrate the clinical implications and aid patients and surgeons in choosing the most suitable method.

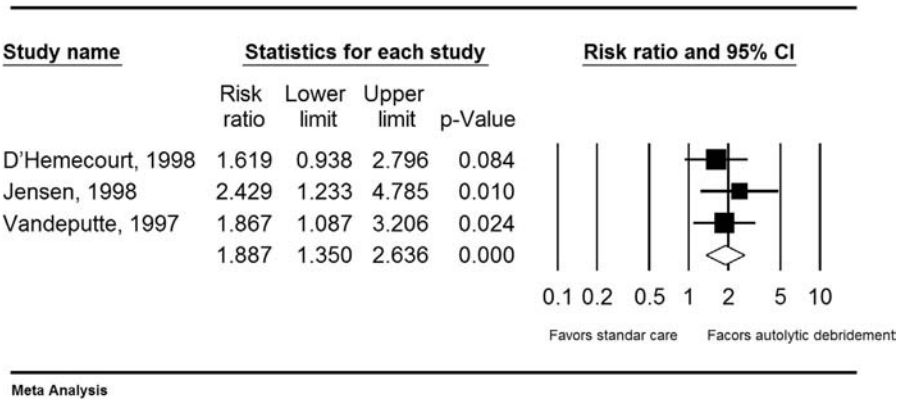

Fig 2. Autolytic débridement vs conventional wound care. The *solid squares* indicate the risk ratio and are proportional to the weights used in the meta-analysis. The *diamond* indicates the pooled risk ratio, and the *lateral tips* of the *diamond* indicate the associated 95% confidence intervals (*CIs*). The *horizontal lines* represent the 95% CIs.

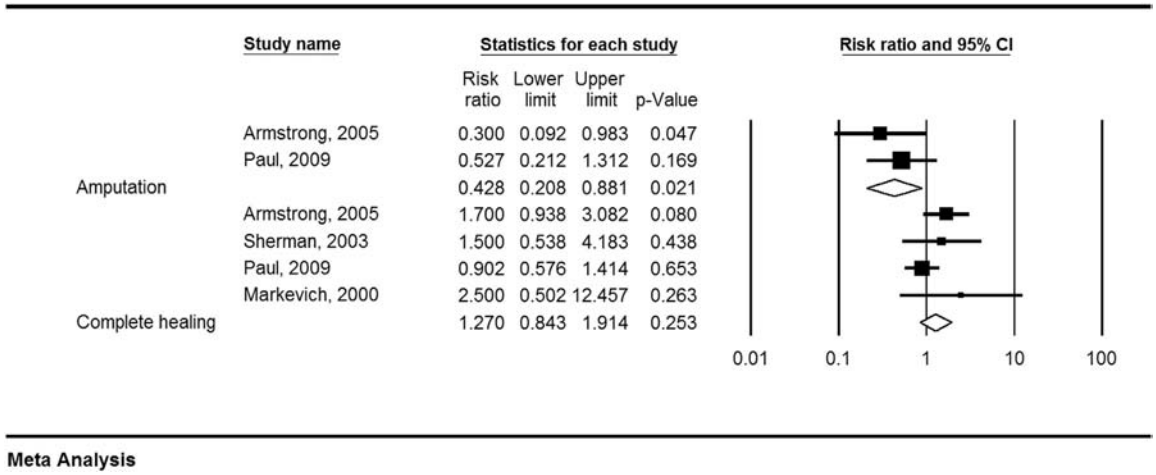

Fig 3. Larval débridement vs conventional wound care. The *solid squares* indicate the risk ratio and are proportional to the weights used in the meta-analysis. The *diamond* indicates the pooled risk ratio, and the *lateral tips* of the *diamond* indicate the associated 95% confidence intervals (*CIs*). The *horizontal lines* represent the 95% CIs.

CONCLUSIONS

The available literature supports the efficacy of several débridement methods, including surgical, autolytic, and larval débridement. Comparative effectiveness evidence between these methods and supportive evidence for other methods is of low quality due to methodologic limitations and imprecision. Hence, the choice of débridement method at the present time should be based on the available expertise, patient preferences, the clinical context, and cost.

AUTHOR CONTRIBUTIONS

Conception and design: TE, JD, GP, AT, MN, RF, RH, BF, LP, MM
Analysis and interpretation: TE, MM
Data collection: TE, JD, GP, AT, MN, RF, RH, BF, LP, MM
Writing the article: TE, JD, GP, AT, MN, RF, RH, BF, LP, MM
Critical revision of the article: TE, JD, GP, AT, MN, RF, RH, BF, LP, MM
Final approval of the article: TE, JD, GP, AT, MN, RF, RH, BF, LP, MM
Statistical analysis: MM
Obtained funding: MM
Overall responsibility: MM

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Submitted Sep 8, 2015; accepted Oct 8, 2015.

Additional material for this article may be found online at www.jvascsurg.org.

APPENDIX (online only).

Data sources and search strategies

A comprehensive search of several databases from each database's earliest inclusive dates to October 2011 (any language, any population) was conducted. The databases included Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid Embase, Ovid Cochrane Database of Systematic Reviews, Ovid Cochrane Central Register of Controlled Trials, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principle investigator. Controlled vocabulary supplemented with keywords was used to search for the topic: diabetic foot débridement, limited to randomized and nonrandomized studies.

Actual search strategy

OVID. Databases: Embase, 1988 to 2011 week 40; Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE 1948 to present; EBM Reviews-Cochrane Central Register of Controlled Trials, 4th quarter 2011; EBM Reviews-Cochrane Database of Systematic Reviews 2005 to October 2011

Search Strategy:

#	*Searches*	*Results*
1	exp Debridement/	28816
2	debridement.mp.	43237
3	1 or 2	43237
4	((diabetic or diabetes) adj3 (foot or feet)).mp.	14923
5	exp Diabetic Foot/	11805
6	4 or 5	14923
7	3 and 6	1582
8	exp controlled study/	3639965
9	exp evidence based medicine/	518676
10	Evidence-based.mp.	176011
11	((control$ or randomized) adj2 (study or studies or trial or trials)).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	4669205
12	meta analysis/	87758
13	meta-analys$.mp.	139596
14	exp "systematic review"/	44105
15	systematic review$.mp.	98714
16	exp Guideline/ or exp Practice Guideline/	271941
17	Guideline$.ti.	87231
18	or/8-17	5189162
19	exp case study/	1572995
20	exp Cohort Studies/	1330764
21	exp longitudinal study/	880349
22	exp retrospective study/	628418
23	exp prospective study/	532053
24	exp observational study/	23108
25	exp comparative study/	2198792
26	exp clinical trial/	1477519
27	exp evaluation/	1088304
28	exp twins/	39276
29	exp validation study/	28010
30	exp experimental study/ or exp field study/ or exp in vivo study/ or exp panel study/ or exp pilot study/ or exp prevention study/ or exp quasi experimental study/ or exp replication study/ or exp theoretical study/ or exp trend study/	6878167
31	((clinical or evaluation or twin or validation or experimental or field or "in vivo" or panel or pilot or prevention or replication or theoretical or trend or comparative or cohort or longitudinal or retrospective or prospective or population or concurrent or incidence or follow-up or observational) adj (study or studies or survey or surveys or analysis or analyses or trial or trials)).mp.	6826566
32	("case study" or "case series" or "clinical series" or "case studies").mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	154892
33	or/19-32	12888585
34	7 and (18 or 33)	1023
35	from 7 keep 919-1503	585
36	limit 35 to (clinical trial or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or twin study) [Limit not valid in Embase, CDSR; records were retained]	105
37	34 or 36	1023
38	Limit 37 to (book or book series or editorial or erratum or letter or note or addresses or autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase, Ovid MEDLINE, Ovid MEDLINE In-Process, CCTR, CDSR; records were retained]	60

(*Continued on next page*)

Continued.

#	*Searches*	*Results*
39	37 not 38	963
40	from 7 keep 1504-1582	79
41	39 or 40	992
42	remove duplicates from 41	662

Scopus.

1 TITLE-ABS-KEY ((diabetes w/3 foot) or (diabetic w/3 foot) or (diabetes w/3 feet) or (diabetic w/3 feet))
2 TITLE-ABS-KEY (debridement)
3 TITLE-ABS-KEY ((evidence W/1 based) or (meta W/1 analys*) or (systematic* W/2 review*) or guideline or (control* W/2 stud*) or (control* W/2 trial*) or (randomized W/2 stud*) or (randomized W/2 trial*))
4 TITLE-ABS-KEY ("comparative study" or "comparative survey" or "comparative analysis" or "cohort study" or "cohort survey" or "cohort analysis" or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "retrospective study" or "retrospective survey" or "retrospective analysis" or "prospective study" or "prospective survey" or "prospective analysis" or "population study" or "population survey" or "population analysis" or "concurrent study" or "concurrent survey" or "concurrent analysis" or "incidence study" or "incidence survey" or "incidence analysis" or "follow-up study" or "follow-up survey" or "follow-up analysis" or "observational study" or "observational survey" or "observational analysis" or "case study" or "case series" or "clinical series" or "case studies" or "clinical study" or "clinical trial" or "evaluation study" or "evaluation survey" or "evaluation analysis" or "twin study" or "twin survey" or "twin analysis" or "validation study" or "validation survey" or "validation analysis" or "experimental study" or "experimental analysis" or "field study" or "field survey" or "field analysis" or "in vivo study" or "in vivo analysis" or "panel study" or "panel survey" or "panel analysis" or "pilot study" or "pilot survey" or "pilot analysis" or "prevention study" or "prevention survey" or "prevention analysis" or "replication study" or "replication analysis" or "theoretical study" or "theoretical analysis" or "trend study" or "trend survey" or "trend analysis")
5 1 and 2 and (3 or 4)
6 PMID(0*) or PMID(1*) or PMID(2*) or PMID(3*) or PMID(4*) or PMID(5*) or PMID(6*) or PMID(7*) or PMID(8*) or PMID(9*)
7 5 and not 6
8 DOCTYPE(le) or DOCTYPE(ed) or DOCTYPE(bk) or DOCTYPE(er) or DOCTYPE(no) or DOCTYPE(sh)
9 7 and not 8

A systematic review and meta-analysis of adjunctive therapies in diabetic foot ulcers

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Background: **Multiple adjunctive therapies have been proposed to accelerate wound healing in patients with diabetes and foot ulcers. The aim of this systematic review is to summarize the best available evidence supporting the use of hyperbaric oxygen therapy (HBOT), arterial pump devices, and pharmacologic agents (pentoxifylline, cilostazol, and iloprost) in this setting.**

Methods: **We searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and Scopus through October 2011. Pairs of independent reviewers selected studies and extracted data. Predefined outcomes of interest were complete wound healing and amputation.**

Results: **We identified 18 interventional studies; of which 9 were randomized, enrolling 1526 patients. The risk of bias in the included studies was moderate. In multiple randomized trials, the addition of HBOT to conventional therapy (wound care and offloading) was associated with increased healing rate (Peto odds ratio, 14.25; 95% confidence interval, 7.08-28.68) and reduced major amputation rate (odds ratio, 0.30; 95% confidence interval, 0.10-0.89), compared with conventional therapy alone. In one small trial, arterial pump devices had a favorable effect on complete healing compared with HBOT and in another small trial compared with placebo devices. Neither iloprost nor pentoxifylline had a significant effect on amputation rate compared with conventional therapy. No comparative studies were identified for cilostazol in diabetic foot ulcers.**

Conclusions: **There is low- to moderate-quality evidence supporting the use of HBOT as an adjunctive therapy to enhance diabetic foot ulcer healing and potentially prevent amputation. However, there are only sparse data regarding the efficacy of arterial pump devices and pharmacologic interventions. (J Vasc Surg 2016;63:46S-58S.)**

Foot ulcers are a major complication of diabetes and are associated with a substantial burden for the patients and the entire health care system.[1] Multiple factors are involved in the etiology of diabetic foot ulcers, the main ones being peripheral neuropathy, external trauma, and peripheral vascular disease.[2]

From the Evidence-based Practice Center,[a] Mayo Clinic Libraries,[e] and Division of Preventive, Occupational and Aerospace Medicine,[g] Mayo Clinic, Rochester; the Second Medical Department, Aristotle University, Thessaloniki[b]; the Unidad de Conocimiento y Evidencia, Universidad Peruana Cayetano Heredia, Lima[c]; the Department of Internal Medicine, University of Missouri, Columbia[d]; and the Department of Surgery, Lutheran Medical Center, Brooklyn.[f]

This review was partially funded by a contract from the Society for Vascular Surgery, which had no involvement in the study design; collection, analysis, and interpretation of data; manuscript writing; or the decision to submit the manuscript for publication.

Author conflict of interest: none.

Additional material for this article may be found online at www.jvascsurg.org.

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Independent peer review and oversight has been provided by members of the Society for Vascular Document Oversight Committee: Peter Gloviczki, MD (Chair), Martin Bjorck, MD, Ruth Bush, MD, Thomas Forbes, MD, Michel Makaroun, MD, Gregory Moneta, MD.

0741-5214

http://dx.doi.org/10.1016/j.jvs.2015.10.007

Several therapies have been proposed as adjuncts to traditional wound care (dressing changes, offloading, and débridement) to improve tissue oxygenation and enhance the healing process. To aid clinicians and patients in the process of decision making and choosing the best approach for managing diabetic foot ulcers, the Society for Vascular Surgery selected a priori several adjunct therapies that require a systematic review to summarize the best available evidence.

These therapies are hyperbaric oxygen therapy (HBOT), with the possible physiologic effects of reducing regional and local ischemia, stimulation of oxygen-dependent components of wound repair, release of bone marrow stem cells, enhancing host antimicrobial responses, and stimulation of angiogenic healing responses to the point of local host competency; pharmacologic agents that improve oxygenation by causing vasodilatation; and pneumatic compression devices that aim at augmenting distal regional blood flow.[3-6] In this systematic review, we sought to identify and summarize the best available evidence that supports the use of these therapies and estimate the magnitude of benefit in patient-important outcomes.

METHODS

The systematic review was based on a prespecified protocol approved by a committee from the Society for

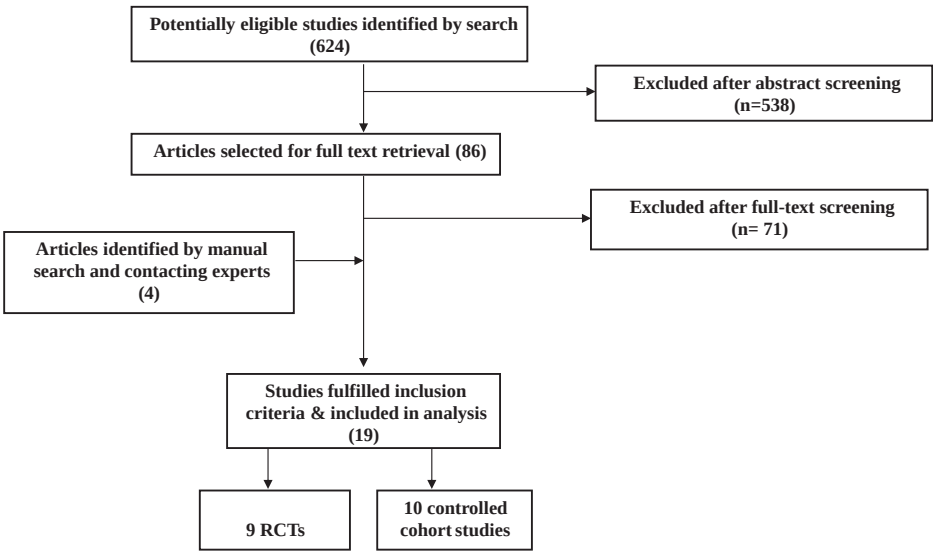

Fig 1. Flow diagram shows how studies were screened and selected. *RCT,* Randomized controlled trial.

Vascular Surgery and is being reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[7]

Eligibility criteria. Eligible studies were randomized trials and controlled observational studies in patients with diabetic foot ulcers in which a discrete list of adjunctive therapies was compared with other adjunctive therapies or with a control group and reported the outcomes of interest. The control group is a group of patients in the same study that received comprehensive wound care (dressing changes, offloading, and débridement) but did not receive the intervention being tested. The control group could be contemporary or historical, matched or unmatched, realizing that historical and unmatched control groups offer weaker inference. The interventions we evaluated were HBOT, arterial pump device, and pharmacologic agents (pentoxifylline, cilostazol and iloprost). We were interested in studies that assessed the effect of the intervention on patient-important outcomes[8] such as rate of complete wound healing and major amputation. Studies were included regardless of language, size, or duration of patient follow-up. We excluded nonoriginal studies, such as review articles, commentaries, and letters, and uncontrolled studies (single-arm cohorts).

Study identification. The search strategy was designed and conducted by an experienced reference librarian (L.P.) with input from the study's principle investigator (M.H.M.). We used controlled vocabulary (eg, Medical Subject Headings terms) with keywords to define the concepts of adjunctive therapy and diabetic foot. We conducted a comprehensive search of several databases from each database's earliest inclusive dates to October 2011. Databases included were Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid Embase, Ovid Cochrane Database of Systematic Reviews, Ovid Cochrane Central Register of Controlled Trials, and Scopus. We identified additional candidate studies by review of the bibliographies f included articles and contact with experts. The detailed search strategy is available in the Appendix (online only).

Study selection and data collection. All relevant abstracts were downloaded into an endnote library and uploaded into an online reference management system (DistillerSR; Evidence Partners, Ottawa, ON, Canada). Reviewers working independently and in duplicate screened the abstracts for eligibility. Included abstracts were screened in full text. When reviewers disagreed on including an abstract, the full-text article was automatically reviewed. Full-text screening was also done in duplicate (Fig 1). Disagreements at this level were resolved by discussion and consensus. We calculated the inter-reviewer agreement beyond chance (κ) during the full-text screening level. Descriptive, methodologic, and outcome data were abstracted from eligible studies using a standardized piloted Web-based form.

For each study, at least one reviewer abstracted the following descriptive data: detailed description of baseline characteristics (main demographic characteristics, type and duration of diabetes, size and duration of the ulcer, etc) and interventions received (active or control) for all participants enrolled. We also collected quality assessment and outcome data. Another reviewer checked the entered data for accuracy and resolved inconsistencies by referring to the full-text article.

Risk of bias assessment. Two reviewers independently assessed the quality of studies included. Nonrandomized studies were evaluated using the Newcastle-Ottawa scale,[9] and we assessed outcome ascertainment, adjustment for confounders, proportion of patients lost to follow-up, and sample selection in each study. Randomized trials were evaluated using the Cochrane risk of bias assessment tool.[10] Domains assessed included randomization, blinding,

Table I. Characteristics of the included studies

Study	*No.*	*Groups*	*Age, years*	*Male, %*	*T2D/T1D*	*Duration of diabetes, year*	*HbA_{1c}, %*	*Ulcer description*	*Follow-up, months*
Abidia,[27] 2003	18	HBOT	72	50	NR	13	<8.5 (all patients)	Size: 1.06 cm^2 Duration: 6 months All patients grade 1	12
		Control	70			11		Size 0.78 cm^2 Duration: 9 months All patients grade 2	
Armstrong,[5] 2000	115	Arterial pump device	49	74	NR	12.5	9.7 ± 1.9	Size: 6.7 cm^2	1.5
		Placebo	51			12.7	9.2 ± 2.5	Size: 7.5	
Ay,[28] 2004	50	HBOT	57	66	NR	16.1 ± 3.2	9.1	NR	1
		Standard care	60			15.4 ± 2.7	7.8		
Baroni,[29] 1987	28	HBOT	58	60.7	13/15	16.4 ± 6.8	8.8 ± 1.2	Size: 33.4 ± 28.9	13.5
		Standard care	59			13.9 ± 6		Size: 28.1 ± 21.9	
Doctor,[3] 1992	30	HBOT	56	70	83/17	10	NR	NR	1.5
		Standard care	60			11			
Duzgun,[30] 2008	100	HBOT	58	64	14/86	17	8.0 ± 1.9	According to Wagner's Classification: Grade 2: 6 patients Grade 3: 19 patients Grade 4: 25 patients	23 ± 3
		Standard care	63			16	8.7 ± 2.9	Grade 2: 12 patients Grade 3: 18 patients Grade 4: 20 patients	
Faglia,[31] 1996	70	HBOT	62	71	NR	16	9.3 ± 2.5	According to Wagner's classification: Grade 2: 4 patients Grade 3: 9 patients Grade 4: 22 patients	2
		Standard care	66			19	8.5 ± 2.3	Grade 2: 5 patients Grade 3: 8 patients Grade 4: 20 patients	
Faglia,[32] 1998	115	HBOT	51	73	NR	17	8.8 ± 2.3	According to Wagner's classification: Grade 2: 13 patients Grade 3: 32 patients Grade 4: 70 patients	NR
		Standard care	65						
Kalani,[33] 2002	38	HBOT	60	79	44/54	27	7.1	Size: 10.77 cm^2	36
		Standard care					7.3	Size: 4.49 cm^2	
Kessler,[34] 2003	28	HBOT	60	68	85/15	18.2 ± 6.6	9.4 ± 2.4	Size: 2.31 cm^2	1
		Standard care					8.1 ± 1.4	Size: 2.82 cm^2	
Londahl,[35] 2010	94	HBOT	61	81	67/33	20	7.8	Size: 3.5 cm^2	12
		Placebo	69			23	8.1	Size: 2.8 cm^2	
Margolis,[16] 2013	6259	HBOT	793	62	64	Not available	Not available	≥3: 46%	767,060 person-days of wound care
		Standard care	5466	63	56	Not available	Not available	≥3: 18%	
Oriani,[17] 1990	80	HBOT	53	60	NR	14.5 ± 9.6	9.5	NR	NR

(*Continued on next page*)

Table I. Continued.

Study	*No.*	*Groups*	*Age, years*	*Male, %*	*T2D/T1D*	*Duration of diabetes, year*	*HbA_{1c}, %*	*Ulcer description*	*Follow-up, months*
		Standard care	58			16.1 ± 6.4	8.2		
Ramani,[4] 1993	40	Pentoxifylline	59	NR	NR	11.5	NR	According to Wagner's Classification: Grade 2: 2 patients Grade: 6 patients Grade: 10 patients Grade: 2 patients	3
		Standard care	62			12.5		Grade: 2 patients Grade: 6 patients Grade: 12 patients	
Sert,[19] 2008	60	Iloprost	62	60	100/0	15	10.4 ± 2.1	Duration: 2.3 months	1
		Standard care				14	10.8 ± 2.3		
Sousa,[36] 2005	95	HBOT	64	70.8	82/18	20	NR	According to Wagner's classification: Grade 2: 8 patients Grade 3: 11 patients Grade 4: 36 patients	50
		Standard care	61			22		Grade 2: 4 patients Grade 3: 9 patients Grade 4: 28 patients	
Stone,[37] 1995	469	HBOT	NA	NA	NA	NA	NA	Size: 25.33 ± 0.98	NA
		Standard care						Size: 11.99 ± 0.61	
Wang,[18] 2011	86	HBOT	62	NR	NR	20 ± 10	8.1 ± 1.8	Size: 7 cm^2	11
		ESWT	61	NR	NR	16.1 ± 6.4	8.7 ± 2.2	Size: 4 cm^2	14
Zamboni,[38] 1997	10	HBOT	63	75	0/100	>10	NR	Size: 6.0 cm^2	4-6
		Standard care	54					Size: 4.4 cm^2	

ESWT, Extracorporeal shockwave therapy; *HbA_{1c},* glycated hemoglobin; *HBOT,* hyperbaric oxygen therapy; *NA,* not available; *NR,* not reported; *T2D/T1D,* type 2 diabetes/type 1 diabetes.

allocation concealment, baseline imbalances, loss to follow-up, and bias due to funding. The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods.[11,12] Following this approach, randomized trials are considered to warrant high quality of evidence (ie, high certainty) and observational studies warrant low quality of evidence. The evidence grading can be increased (if a large effect is observed) or decreased if other factors are noted such as studies being at increased risk of bias or imprecise (small with wide confidence intervals [CIs]).

Statistical analysis. We estimated from each study Peto odds ratios (ORs) with the 95% CI due to the small number of events. Between-studies heterogeneity was calculated by the I^2 statistic, which estimates the proportion of variation in results across studies that is not due to chance.[13] Meta-analysis was completed using Comprehensive Meta-Analysis 2.2 software (Biostat Inc, Englewood, NJ).

Data were insufficient to perform subgroup analysis. Evaluation of publication bias was not feasible due to the small number of included studies per comparison.[14]

RESULTS

Search results and included studies. The literature search yielded 624 potentially relevant abstracts. After abstract screening, we excluded 538 studies and retrieved 86 articles in full text. Fifteen articles fulfilled our inclusion criteria and were eligible for data extraction. We identified three additional articles by manually searching the bibliographies of the included articles to a total of 18 articles, of which 12 reported sufficient data for meta-analyses (Fig 1). The identified studies included nine randomized controlled trials (RCTs) and nine controlled cohorts, including data from 1526 patients with diabetic foot ulcers who received some sort of an adjunctive therapy. The characteristics of included studies are described in Table I. The interventions are described in detail in Table II. The adjusted agreement between reviewers (κ) averaged 0.82 as calculated by the online system. Experts from the Society for Vascular Surgery continued to monitor the literature after the search date for new studies that may affect the diabetic foot ulcer guidelines. They identified one additional systematic review and meta-analysis,[15] with a search date of April 20, 2012, and one additional large observational study,[16] both of which addressed the efficacy of HBOT.

Methodologic quality and risk of bias. The quality of the included studies ranged from low to moderate. Randomization and allocation concealment were adequately described in only six and two of nine RCTs, respectively. In three RCTs,

Table II. Objectives, inclusion criteria, and interventions of each study

Study ID	*Objective*	*Inclusion and exclusion criteria*	*Treatment in group 1*	*Treatment in group 2*
Abidia,[27] 2003	To evaluate the role of HBOT in the management of these ulcers.	Patients were included if they had an ulcer >1 cm and <10 cm in maximum diameter which had not shown any signs of healing, despite optimum medical management for >6 weeks since presenting. Patients for whom vascular surgery, angioplasty, or thrombolysis was planned were excluded. Occlusive arterial disease was confirmed by an ankle-brachial pressure index <0.8. Acceptable metabolic control of their diabetes was judged by glycated hemoglobin level of <8.5%.	HBOT: hyperbaric 100% oxygen. The treatment was given in a multiplace chamber via hood at a pressure of 2.4 atm abs for 90 minutes daily, 5 days/week, totalling 30 sessions. Medical management was optimized and equivalent for all patients in both groups.	Control group: hyperbaric air with the same specification as the treatment group in addition to the standard medical management.
Armstrong,[5] 2000	To evaluate the proportion of healing of foot infections in subjects with diabetes undergoing aggressive edema reduction with the use of intermittent pneumatic foot compression after foot-level débridement.	The study included patients with diabetes who had foot infections requiring incision and débridement. They excluded patients with diagnosed active congestive heart failure, end-stage renal disease, or a serum creatinine level >177 μmol/L (>2.0 mg/dL) on the day of hospital admission. They also excluded any subjects who received a lower extremity bypass graft within the period of study.	Functioning pulsatile pneumatic foot compression system. This system includes a wrap that goes around the foot and a pneumatic pump that intermittently fires bursts of air through tubing to the wrap. The wrap contains a bladder that is rapidly inflated to ~160 mm Hg for 2 seconds to empty the veins of the foot. This cycle is repeated every 20 seconds.	Placebo pulsatile pneumatic foot compression system with the same specifications. In the placebo device, all lights, audible alerts, and programming indicators were functional and identical to and indistinguishable from those of the active device. The placebo foot wrap that was applied to the foot, however, was fenestrated so as not to inflate and impart compression. Because all patients who participated in this project had moderate to severe peripheral sensory neuropathy, they were not generally able to feel whether they were receiving substantial compression therapy.
Ay,[28] 2004	To study the therapeutic efficiency of HBOT by measuring $TcPo_2$ and $TcPco_2$ in patients who had wounds caused by diabetes mellitus.	Diabetic patients with diabetic wound. Patients with untreated pneumothorax were excluded from the study.	HBOT + standard diabetes and wound management + pentoxifylline, Ginkgo glycosides, and ascorbic acid.	Standard diabetes and wound management + pentoxifylline, Ginkgo glycosides, and ascorbic acid.
Baroni,[29] 1987	To study the effect of HBOT in diabetic foot ulcers.	Diabetic patients with ulcers or necrotic foot lesions.	Combined therapeutic regimen consisting of HBO, strict metabolic control, and daily débridement.	Standard care. The same except for HBOT.
Doctor,[3] 1992	To study the effect of HBOT in chronic diabetic foot lesions.	Diabetic patients with chronic foot lesions.	HBOT was administered in a monoplace HBO chamber at atmosphere pressure for 45 minutes for 4 separate sessions over a period of 2 weeks. In addition patients received conventional wound therapy.	Standard care.

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Table II. Continued.

Study ID	*Objective*	*Inclusion and exclusion criteria*	*Treatment in group 1*	*Treatment in group 2*
Duzgun,[30] 2008	To study the use of HBOT vs standard therapy for the treatment of foot ulcers in diabetic patients.	Diabetic patients were considered eligible if they were ≥18 years and if they had a foot wound that had been present for at ≥4 weeks despite appropriate local and systemic wound care.	Standard therapy plus HBOT group standard therapy was supplemented by HBOT administered at a maximum working pressure of 2 ATA, using a unichamber pressure room using a volume of 10 m^3 at 2 to 3 ATA for 90 minutes. Treatment was administered as 2 sessions per day, followed by 1 session on the following day, alternating throughout the course of therapy, which typically extended for 20 to 30 days.	Standard treatment, which is daily wound care, including dressing changes and local débridement at bedside or in the operating room, as well as amputation when indicated.
Faglia,[31] 1996	To evaluate the effectiveness of the systemic HBOT in addition to a comprehensive protocol in decreasing major amputation rate in diabetic patients hospitalized for severe foot ulcer.	Diabetic patients consecutively hospitalized for foot ulcer.	HBOT group received pure oxygen in multiplace hyperbaric chamber, pressurized with air. Pressure was 2.5 ATA and then dropped to 2.4 to 2.2 ATA. They received daily sessions of 90 minutes each.	Patients only received the standard wound care and diabetic management.
Faglia,[32] 1998	To report the evolution that took place in our hospital between the end of the 1970s and the beginning of the 1990s in the prevalence of major amputations in hospitalized diabetic patients with severe foot ulcer and to assess in our cases the prognostic determinants involved in major amputations.	Diabetic patients who were consecutively hospitalized for foot ulcers. No criteria described.	HBOT, breathed pure oxygen in a hyperbaric chamber pressurized with air, and used a soft helmet. The pressure was 2.5 ATA in the first phase. In the second phase, we applied 2.4 to 2.2 ATA.	Standard care.
Kalani,[33] 2002	To investigate the long-term effect of HBOT in treatment of diabetic foot ulcers.	The patients had been referred due to chronic nonhealing foot ulcers. They were included in the study if the foot ulcers did not heal despite the treatment program.	Patients underwent 40 to 60 sessions of HBOT. The daily treatment sessions were given at a pressure of 250 kPa, equivalent to 15 m H_2O, in an acrylic monoplace chamber pressurized with 100% oxygen, allowing the patient to breathe without a mask or hood. Patients also received the standard therapy as the control group.	Control group: All patients were treated with nonweight-bearing protective shoes, orthosis, and improvement of metabolic control, blood pressure, and nutrition. Regular control of off-loading was performed.

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Table II. Continued.

Study ID	*Objective*	*Inclusion and exclusion criteria*	*Treatment in group 1*	*Treatment in group 2*
Kessler,[34] 2003	To study the effect of systemic HBOT on the healing course of nonischemic chronic diabetic foot ulcers.	Included were patients with type 1 and type 2 diabetes admitted for chronic foot ulcers. Their ulcers (depth <2 mm) were characterized by the absence of favorable evolution for at ≥3 months despite the stabilization of glycemia, the absence of clinical local infection, and satisfactory off-loading measures. Exclusion criteria: patients with gangrenous ulcer with severe sepsis, severe arteriopathy ($TcPo_2$ ± 30 mm Hg), with emphysema, proliferating retinopathy, and claustrophobia.	Patients randomized for HBO underwent two 90-minute daily sessions of 100% O_2 breathing in a multiplace hyperbaric chamber pressurized at 2.5 ATA. This regimen lasted 5 days/wk for 2 consecutive weeks. They also received conventional therapy.	The conventional additional treatment was applied to both groups of patients during hospitalization and the ambulatory period. Each patient was provided with an orthopedic device to remove mechanical stress and pressure at the site of the ulcer during walking. The optimization of metabolic control required subcutaneous insulin administration (2 or 3 injections or bedtime treatment) for the majority of patients.
Londahl,[35] 2010	To evaluate whether HBOT improves the health-related quality of life in these patients.	All patients had diabetes and at ≥1 full-thickness wound below the ankle for >3 months. They were previously treated at a diabetes foot clinic for a period of not <2 months. All patients were assessed by a vascular surgeon at the time of inclusion, and only patients with adequate distal perfusion or nonreconstructible peripheral vascular disease were included in the study. Patients with an acute foot infection were included when the acute phase was resolved. Oral or local antibiotic treatment did not exclude patients from study participation. Exclusion criteria for study participation were contraindications for HBOT (severe obstructive pulmonary disease, malignancy, and untreated thyrotoxicosis), current drug or alcohol misuse, vascular surgery in the lower limbs within the last 2 months, participation in another study, or suspected poor compliance. All participants provided written informed consent.	HBOT treatment sessions were given in a multiplace hyperbaric chamber 5 days/wk for 8 weeks (40 treatment sessions). Study treatment was given as an adjunct to regular treatment at the multidisciplinary diabetes foot clinic, which included treatment of infection, revascularization, débridement, off-loading, and metabolic control according to high international standards	Patients received hyperbaric air through separate double-blinded pipes at the same frequency as HBOT. Study treatment was given as an adjunct to regular treatment at the multidisciplinary diabetes foot clinic, which included treatment of infection, revascularization, débridement, off-loading, and metabolic control according to high international standards
Margolis,[16] 2013	To compare the effectiveness of HBOT with other conventional therapies administered in a wound care network for the treatment of a diabetic foot ulcer and prevention of lower extremity amputation.	Treated between November 2005 and May 2011 by a provider with contractual agreement with HBOT facility, agreed to provide data for research, have diabetes, have adequate lower extremity arterial flow (as determined by the clinician), have a wound on plantar foot (hindfoot, heel, midfoot, or forefoot, toes), experienced failure to heal during the first 4 weeks of wound center care and experienced failure of decrease in wound size by at least 40%.	HBOT	Standard care.
Oriani,[17] 1990	To report the effect of HBOT on diabetic foot ulcers.	Diabetic patients who were consecutively hospitalized for foot ulcers. No criteria described.	HBOT in a hyperbaric chamber at 2.8 ATA and then at 2.5 ATA 6 days/wk until the beginning of granulation and them 5 days/wk until recovery.	Standard care.
Ramani,[4] 1993	To study the effect of pentoxifylline in ischemic diabetic wounds.	Patients with diabetic ischemic ulcer grade ≥2. All patients had evidence of peripheral vascular disease. Neurotrophic ulcers were excluded.	Oral pentoxifylline, 400 mg, 3 times daily, + conventional therapy.	Conventional therapy.

(*Continued on next page*)

Table II. Continued.

Study ID	*Objective*	*Inclusion and exclusion criteria*	*Treatment in group 1*	*Treatment in group 2*
Stone,[37] 1995	To test the hypothesis that a defined course of intermittent increased tissue oxygenation will result in a reduction of amputation rate.	Consecutive patients with diabetic wounds treated at a referral wound center. No further criteria available.	HBOT, 100% oxygen at a greater than normal sea level atmospheric pressure.	Standard care.
Sert,[19] 2008	To assess the efficiency of iloprost (an analog of prostacyclin) infusion on endothelial functions and amputation rate in diabetic foot ulcers with complicated macroangiopathy.	Patients with type 2 diabetes mellitus and severe peripheral ischemic foot ulcer unsuitable for revascularization hospitalized for treatment. The study excluded patients who had septic shock, renal and liver failure, decompensated heart failure, acute or subacute coronary syndromes, active peptic ulcer, acute cerebral hemorrhage, using anticoagulant drug and a known contraindication to iloprost.	Patients were administered iloprost with a dose of 0.5 to 2 ng/kg/min over 6-h infusions for 10 consecutive days.	Patients only received the standard wound care and diabetic management.
Sousa,[36] 2005	To evaluate the long-term clinical evolution of chronic ulcers on lower limbs of patients with diabetes that could not heal with HBOT.	Diabetic patients with infected postsurgical wounds or neuroischemic ulcers in lower limbs (grade 2 or 4 according to Wagner classification) with at least 1 month of evolution and who had received usual care previously with drugs and/or surgery, including arterial revascularization if required	HBOT	Standard care.
Wang,[18] 2011	To compare the effectiveness of ESWT and HBOT in chronic diabetic foot ulcers.	Inclusion criteria: patients with chronic nonhealing diabetic foot ulcers for >3 months' duration. Exclusion criteria: patients with cardiac arrhythmia or a pacemaker, pregnancy, skeletal immaturity, patients with malignancy, and patients lacking complete follow-up data.	HBOT was performed with patients in a sealed multiplace chamber at a pressure of 2.5 ATA. Air pressure was gradually increased from 1 ATA to 2.5 ATA over a 15-minuute interval. HBO was performed daily, 5 times/wk, for a total of 20 treatments. After HBOT, patients resumed their initial wound care protocol including off-loading on the affected foot, wound cleansing with sterile normal saline solution, and application of silver sulfadiazine cream.	ESWT: The treatment dosage was ulcer-size dependent with the numbers of impulses equal to the treatment area in cm^2 ×8, with a minimum of 500 impulses at energy setting E2 (equivalent to 0.23 mJ/mm^2 energy flux density) at a rate of 4 shocks/s. The treatments were conducted 2 times/wk for 3 weeks for a total of 6 treatments. After ESWT, patients resumed their initial wound care protocol including off-loading on the affected foot, wound cleansing with sterile normal saline solution, and application of silver sulfadiazine cream.
Zamboni,[38] 1997	To evaluate the effect of HBOT on the healing of diabetic lower extremity wounds.	Type 1 diabetic patients with chronic nonhealing lower extremity wounds.	HBOT consisting of 100% oxygen for 120 minutes per at a depth of 2.0 ATA. Patients were treated 5 days/wk for a total of 30 treatments. All patients seen weekly in the clinic for wound assessment. In addition patients received the standard wound care and diabetic management.	Patients only received the standard wound care and diabetic management.

ATA, Atmospheres absolute; *ESWT,* extracorporeal shock wave therapy; *HBO,* hyperbaric oxygen; *HBOT,* hyperbaric oxygen treatment; $TcPco_2$, transcutaneous partial pressure of carbon dioxide; $TcPo_2$, transcutaneous partial pressure of oxygen.

Table III. Risk of bias assessment in randomized trials

Study ID	*Randomization methods*	*Concealed allocation*	*Blinding*	*Baseline imbalance*	*Efficient follow-up*	*Adherence to treatment*	*Lost of follow-up. %*	*Funding source*
Abidia,[27] 2003	NR	Sealed envelopes	Yes, double-blinded	No	Regular clinic visits	NR	11.1	NR
Armstrong,[5] 2000	Computerized table	NR	Yes, double blinded	No	Regular clinic visits	Yes	15.6	For-profit
Doctor,[3] 1992	NR	NR	NR	No	Hospitalized	NR	0	Not for-profit
Duzgun,[30] 2008	Random number table	No	NR	No	Regular clinic visits	NR	0	NR/unclear
Faglia,[31] 1996	Randomization table	NR	NR	No	Hospitalized	Yes	2.8	NR
Kessler,[34] 2003	Randomization table	NR	Yes, physicians	No	Hospitalization for 2 weeks then regular clinic visits for 2 weeks	NR	3.5	Not for-profit
Londahl,[35] 2010	In blocks of 10	Sealed envelopes	Yes, double blinded	No	Regular clinic visits	NR	11.7	Not for-profit
Sert,[19] 2008	NR	NR	NR	No	Hospitalized	Yes	0	NR
Wang,[18] 2011	Computer-generated block labels	NR	No	No	Regular clinic visits	NR	10.5	Not for-profit

NR, Not reported.

the patients the physicians were both blinded. In one RCT, only the physicians were blinded. Details of blinding were not reported in the remaining RCTs. No baseline imbalances were mentioned in any of the studies. The percentage lost to follow-up ranged from 0% to 15.6%, with three studies reporting no losses.

The overall risk of bias in the observational studies was high. Although the samples were representative in most of the studies and follow-up was adequate, no baseline imbalances were mentioned in six of the 10 studies and all but one adjusted for confounders. Many concerns were raised regarding one large observational study by Margolis et al,[16] such as insufficient exposure (small number of HBOT sessions), high loss to follow-up (57%), not using transcutaneous oxygen measurements or other vascular assessment to select patients for HBOT, and selection bias (higher Wagner scores in patients receiving HBOT). Therefore, this study was included in the sensitivity analysis. Tables III and IV describe the quality of included studies.

Meta-analysis. Based on six RCTs, HBOT was associated with increased healing rate (OR, 14.25; 95% CI, 7.08-28.68, $I^2 = 0\%$) and reduced major amputation rate (OR, 0.30; 95% CI, 0.10-0.89, $I^2 = 59\%$) compared with conventional therapy. The quality of this evidence is considered low to moderate, potentially downgraded due to methodologic limitations of the included studies. HBOT was given in most studies at 2.0 to 3.0 atmospheric pressure in daily 90-minute sessions in a monoplace or multiplace chamber. On average, patients received 30 sessions, although a few patients in one study received 60 sessions.

Meta-analysis of the six available observational studies was highly sensitive to study selection. When the older five studies were pooled in the meta-analysis, HBOT was associated with a statistically significant increase in healing rates and with a significant reduction in the amputation rate (Figs 2 and 3). When we added the study by Margolis et al[16] in the sensitivity analysis, the effect on amputation becomes imprecise (OR, 0.58; 95% CI, 0.24-1.40) and on the healing rate becomes reversed (OR, 2.88; 95% CI, 1.14-7.25). Therefore, the true effect should be derived from RCTs because they provide higher-quality evidence (here, moderate). Lastly, we performed a sensitivity analysis for the outcome of amputation, excluding the study by Oriani et al[17] in which it was not possible to distinguish minor from major amputations, and the results were unchanged (OR, 0.35; 95% CI, 0.25-0.50).

Results of individual studies (meta-analysis not feasible). One RCT[18] compared extracorporeal shockwave therapy (ESWT) to HBOT and found statistically significant increase in the wound-healing rate in favor of ESWT (relative risk [RR], 2.34; 95% CI, 1.30-4.21; $P = .003$). ESWT is done as an outpatient procedure, with no anesthesia, through a sterile cellulose barrier, ultrasound gel, and a shockwave applicator. The treatments are given twice weekly for 3 weeks for a total of six treatments. ESWT is hypothesized to induce neovascularization and upregulation of angiogenic growth factors. The quality of evidence is low, downgraded due to methodologic limitations of the study and imprecision (small number of events).

Table IV. Risk of bias assessment in nonrandomized studies

	Selection				*Outcome*		
Study ID	*Representativeness of exposed cohort*	*Ascertainment of exposure*	*Similarity between groups at the baseline*	*Controlled for confounders?*	*Assessment of outcome*	*Enough follow-up length*	*Follow-up adequacy of cohorts*
Ay,[28] 2004	Truly representative	Yes	Yes	No	No description	Yes	Complete
Baroni,[29] 1987	Truly representative	Yes	Yes	No	No description	Yes	Complete
Faglia,[32] 1998	Truly representative	Yes	No, age was significantly different between 2 groups ($P = .05$)	No	No description	Yes	Complete
Kalani,[33] 2002	Truly representative	Yes	No, larger ulcer area in HBO group, older people in conventional group	No	No description	Yes	5 patients died
Margolis,[16] 2013	Possibly not, study did not use $TcPo_2$ measurements or other vascular assessment to select patient for HBOT	Yes, but insufficient exposure (small number of HBOT sessions)	No, higher Wagner scores in patients receiving HBOT	Propensity matching and instrumental variable analysis	No description	Yes	High loss to follow-up (57%)
Oriani,[17] 1990	Truly representative	Yes	Yes	No	No description	NR	Complete
Ramani,[4] 1993	Truly representative	Yes	Yes	No	No description	Yes	3 patients died
Sousa,[36] 2005	Truly representative	Yes	Yes	No	No description	Yes	Complete
Stone,[37] 1995	Truly representative	Yes	No, HBOT group had more serious wounds	No	No description	NR	Complete
Zamboni,[38] 1997	Truly representative	Yes	Yes	No	Blinded	Yes	Complete

HBOT, Hyperbaric oxygen therapy; *NR*, not reported; *$TcPo_2$*, transcutaneous partial pressure of oxygen.

Armstrong et al[5] conducted an RCT and compared arterial pump device to a placebo device and reported a significantly higher proportion of healing in the active group than in the placebo group (RR, 1.47; 95% CI, 1.06-2.03). Quality of evidence is low, downgraded due to methodologic limitations of the study and imprecision (small number of events).

Another RCT[19] comparing iloprost to placebo was identified. It reported no statistically significant difference between the two groups in amputation rates (RR, 0.086; 95% CI, 0.72- 1.02; $P = .097$). The quality of evidence is low, downgraded due to methodologic limitations of the study and imprecision (small number of events).

An observational study by Ramani et al[4] found pentoxifylline was as effective as conventional therapy, with no statistically significant difference in amputation rates between the 2 groups (RR, 0.83; 95% CI, 0.47-1.46). Quality of evidence is low, downgraded due to methodologic limitations of the included study and imprecision (wide CI and small number of events).

No study comparing cilostazol to standard care or any other adjunctive therapy—in the setting of diabetic foot ulcer—was found.

DISCUSSION

We conducted a systematic review and meta-analyses to evaluate the comparative effectiveness of different adjunctive therapies for diabetic foot ulcers. We identified a significant beneficial effect of HBOT compared with standard care in improving the healing rate and reducing the risk of major amputations. This effect was consistent across RCTs and controlled cohorts when analyzed pooled or separately. Nevertheless, the overall quality of the evidence is low to moderate due to several limitations that are associated with the methodologic quality of the studies.

Data from one small RCT suggest that ESWT is better than HBOT in enhancing wound healing.[18] However, the quality of this comparative evidence was low, and this finding needs to be verified in additional future

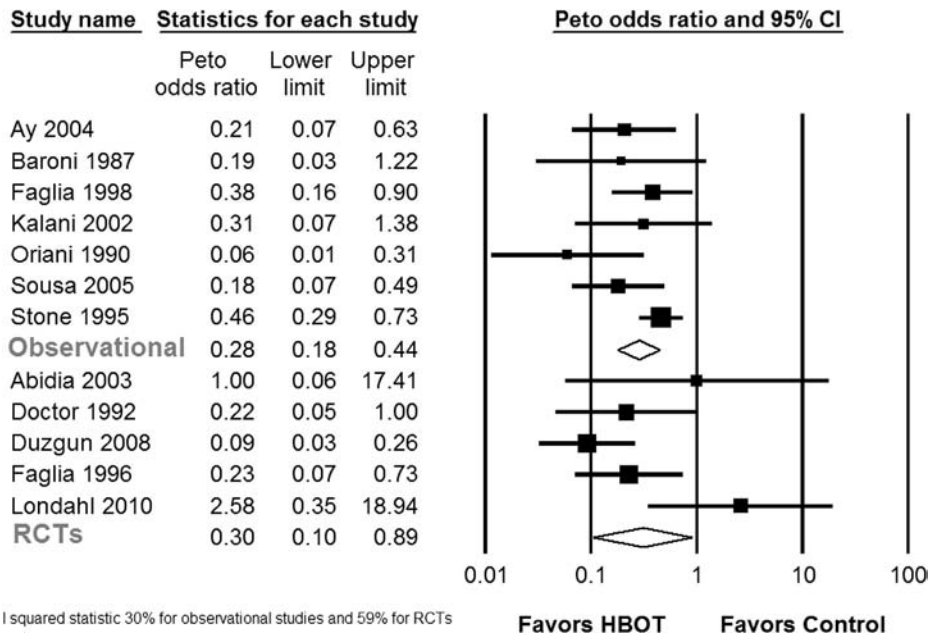

Fig 2. Meta-analysis of major amputation rate. The *solid squares* indicate the odds ratios and are proportional to the weights used in the meta-analysis. The *diamond* indicates the pooled odds ratio, and the *lateral tips* of the *diamond* indicate the associated 95% confidence interval (*CI*). The *horizontal lines* represent the 95% CIs. *HBOT,* Hyperbaric oxygen therapy; *RCT,* randomized controlled trial.

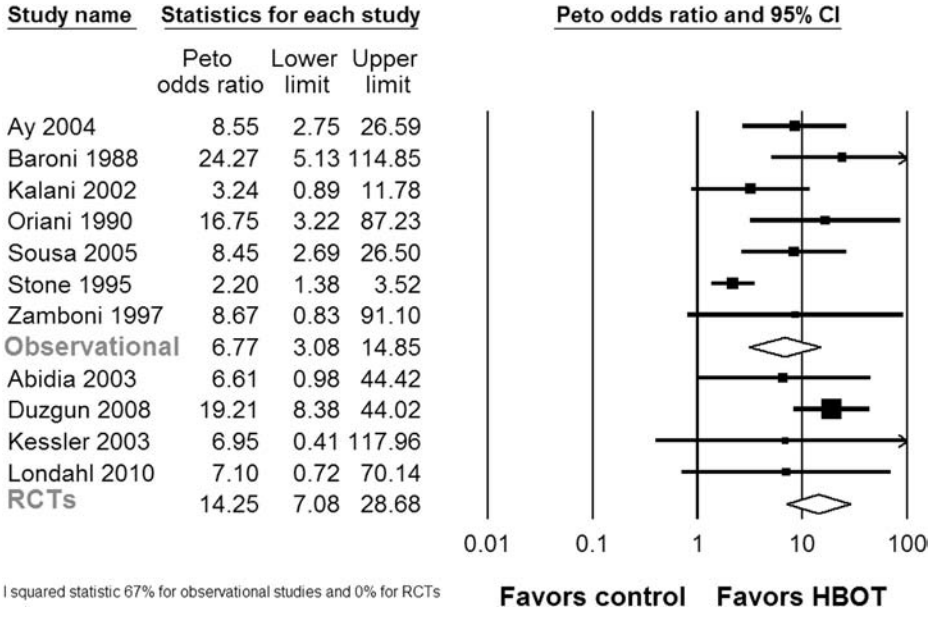

Fig 3. Meta-analysis of healing rate. The *solid squares* indicate the odds ratios and are proportional to the weights used in the meta-analysis. The *diamond* indicates the pooled odds ratio, and the *lateral tips* of the *diamond* indicate the associated 95% confidence interval (*CI*). The *horizontal lines* represent the 95% CIs. *HBOT,* Hyperbaric oxygen therapy; *RCT,* randomized controlled trial.

comparative effectiveness trials. Moreover, there is also only sparse data regarding the effectiveness of arterial pump devices, iloprost, and pentoxifylline; hence, one should verify their effect on patient-important outcomes for diabetic foot ulcers in rigorously designed studies.

In regard to HBOT, our results are consistent with other systematic reviews.[15,20,21] It is important to note, however, that the effect of HBOT on amputation was imprecise in some these reviews when estimated using a RR measure, whereas using Peto OR showed more precise estimates. The sensitivity of conclusions to the choice of the measure of effect used is a sign of imprecision that can lower confidence warranted by this evidence. Although conventional therapy (the comparison arm in most of the included studies in this review) included comprehensive wound care (débridements, wound dressing, and offloading), the way this care was provided was clearly heterogenous across studies.

Our conclusions regarding the benefit of HBOT in diabetic foot setting are consistent with reviews that evaluated its potential role in a variety of other types of chronic wounds.[22,23] Our review updated the evidence base and expanded on previous findings exploring the role of other adjunctive therapies in patients with diabetic foot ulcers.

Clinical and practice implications. There is low- to moderate-quality evidence that suggests a beneficial effect of HBOT when used as an adjunct to standard treatment for diabetic foot ulcers. HBOT should always be used as an adjunctive procedure (along with comprehensive wound care, regular wound monitoring and débridement, and offloading). HBOT is unlikely to be helpful in patients with severe uncorrectable ischemia because oxygen will not reach the ischemic area in a sufficient tension to provoke angiogenesis. The decision to start HBOT should be made after ischemia status is evaluated. In the included studies, it is challenging to tell whether such principles have always been followed or to conduct stratified analysis based on the vascular status. Therefore, the estimates we provide (in increased healing and reduction of major amputations) should be viewed as an average expected effect in a heterogeneous group of patients with diabetic foot ulcers.

Other adjunctive therapy methods need to be further studied using well-designed RCTs to provide enough evidence to support their use in the clinical practice. Evidence of treatments that were shown beneficial in other types of chronic wounds may be extrapolated to the setting of diabetic foot ulcers; for example, patients with critical limb ischemia and nonhealing wounds had improved wound healing and limb preservation by using an intermittent pneumatic compression device.[24] A meta-analysis suggested that negative-pressure therapy is likely effective in the treatment of chronic wounds.[25] A systematic review of negative-pressure therapy specifically in diabetic foot ulcer suggested possible benefit but highlighted the smaller body of evidence in this setting.[26]

The accompanying guidelines by the Society for the Vascular Surgery will supply more details on the various options of adjunctive therapies and their use in different clinical situations, so that the patient and the clinician can both make an informed decision and select the right option according to the given clinical scenario. This systematic review addresses certain a priori chosen adjunctive therapies for diabetic foot ulcers. Other treatments, such as noncontact low-frequency ultrasound therapy, negative-pressure wound therapy, platelet-derived growth factor, various cellular matrix materials and dressings, bioengineered skin substitutes, and split-thickness skin grafting, are not addressed in this report and will be discussed in the guidelines when appropriate.

CONCLUSIONS

There is low- to moderate-quality evidence supporting the use of HBOT as an adjunctive therapy to enhance diabetic foot ulcer healing and prevent amputation. More studies are needed to provide adequate data regarding the effectiveness of arterial pumps and pharmacologic interventions.

AUTHOR CONTRIBUTIONS

Conception and design: TE, AT, GP, JD, RH, BF, MN, LP, AH, PC, LS, MM
Analysis and interpretation: TE, MM
Data collection: TE, AT, GP, JD, RH, BF, MN, LP, AH, PC, LS, MM
Writing the article: TE, AT, GP, JD, RH, BF, MN, LP, AH, PC, LS, MM
Critical revision of the article: TE, AT, GP, JD, RH, BF, MN, LP, AH, PC, LS, MM
Final approval of the article: TE, AT, GP, JD, RH, BF, MN, LP, AH, PC, LS, MM
Statistical analysis: MM
Obtained funding: MM
Overall responsibility: MM

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Submitted Sep 8, 2015; accepted Oct 8, 2015.

Additional material for this article may be found online at www.jvascsurg.org.

APPENDIX (online only).

Data sources and search strategies

A comprehensive search of several databases from each database's earliest inclusive dates to October 2011 (any language, any population) was conducted. The databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Database of Systematic Reviews, Ovid Cochrane Central Register of Controlled Trials, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principle investigator. Controlled vocabulary supplemented with keywords was used to search for the topic: adjunctive therapy for diabetic foot, limited to randomized and nonrandomized studies.

Actual search strategy

OVID. Database(s): Embase 1988 to 2011 Week 40, Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE 1948 to Present, EBM Reviews-Cochrane Central Register of Controlled Trials 4th Quarter 2011, EBM Reviews-Cochrane Database of Systematic Reviews 2005 to October 2011

Search Strategy:

No.	*Searches*	*Results*
1	((diabetic or diabetes) adj3 (foot or feet)).mp.	14925
2	exp Diabetic Foot/	11809
3	1 or 2	14925
4	exp Hyperbaric Oxygenation/	17396
5	hyperbaric oxygen*.mp.	19469
6	exp pentoxifylline/	12889
7	cilostazol.mp.	3684
8	ilioprost.mp.	5
9	iloprost.mp. or exp iloprost/	7387
10	"art-assist".mp.	7
11	((compression or arterial) adj3 (device or pump)).mp.	3594
12	exp cilostazol/	2463
13	(adjuvant or adjunctive).mp.	268148
14	exp Negative-Pressure Wound Therapy/ or "negative pressure".mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	11821
15	"vacuum assisted".mp.	4586
16	exp Hydrogel/ or hydrogel.mp.	22949
17	(moist adj2 therap*).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	96
18	exp platelet derived growth factor/	24972
19	(platelet adj2 "growth factor*").mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	44119
20	exp artificial skin/	2678
21	"artificial skin".mp.	1681
22	or/4-21	395511
23	3 and 22	1434
24	exp controlled study/	3639965
25	exp evidence based medicine/	518786
26	evidence-based.mp.	176190
27	((control$ or randomized) adj2 (study or studies or trial or trials)).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	4670105
28	meta analysis/	87832
29	meta-analys$.mp.	139695
30	exp "systematic review"/	44105
31	systematic review$.mp.	98805
32	exp Guideline/ or exp Practice Guideline/	271973
33	guideline$.ti.	87253
34	or/24-33	5190301
35	exp case study/	1573936
36	exp Cohort Studies/	1332357
37	exp longitudinal study/	881229
38	exp retrospective study/	629108
39	exp prospective study/	532545
40	exp observational study/	23108
41	exp comparative study/	2199767
42	exp clinical trial/	1478242
43	exp evaluation/	1089572
44	exp twins/	39295
45	exp validation study/	28010
46	exp experimental study/ or exp field study/ or exp in vivo study/ or exp panel study/ or exp pilot study/ or exp prevention study/ or exp quasi experimental study/ or exp replication study/ or exp theoretical study/ or exp trend study/	6880306

(*Continued on next page*)

Continued.

No.	*Searches*	*Results*
47	((clinical or evaluation or twin or validation or experimental or field or "in vivo" or panel or pilot or prevention or replication or theoretical or trend or comparative or cohort or longitudinal or retrospective or prospective or population or concurrent or incidence or follow-up or observational) adj (study or studies or survey or surveys or analysis or analyses or trial or trials)).mp.	6829746
48	("case study" or "case series" or "clinical series" or "case studies").mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	155006
49	or/35-48	12895186
50	23 and (34 or 49)	964
51	from 23 keep 814-1331	518
52	limit 51 to (clinical trial or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or twin study) [Limit not valid in Embase, CDSR; records were retained]	126
53	50 or 52	964
54	limit 53 to (book or book series or editorial or erratum or letter or note or addresses or autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase, Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process, CCTR, CDSR; records were retained]	68
55	53 not 54	896
56	from 23 keep 1332-1434	103
57	55 or 56	938
58	remove duplicates from 57	619

Scopus.

1 TITLE-ABS-KEY((diabetes w/3 foot) or (diabetic w/3 foot) or (diabetes w/3 feet) or (diabetic w/3 feet))
2 TITLE-ABS-KEY("hyperbaric oxygen*" or pentoxifylline or cilostazol or ilioprost or iloprost or "art-assist" or (compression w/3 device) or (compression w/3 pump) or (arterial w/3 device) or (arterial w/3 pump) or adjuvant or adjunctive or "negative pressure" or "vacuum assisted" or hydrogel or (moist w/2 therap*) or (platelet w/2 "growth factor*") or "artificial skin")
3 1 and 2
4 TITLE-ABS-KEY((evidence W/1 based) or (meta W/1 analys*) or (systematic* W/2 review*) or guideline or (control* W/2 stud*) or (control* W/2 trial*) or (randomized W/2 stud*) or (randomized W/2 trial*))
5 TITLE-ABS-KEY("comparative study" or "comparative survey" or "comparative analysis" or "cohort study" or "cohort survey" or "cohort analysis" or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "retrospective study" or "retrospective survey" or "retrospective analysis" or "prospective study" or "prospective survey" or "prospective analysis" or "population study" or "population survey" or "population analysis" or "concurrent study" or "concurrent survey" or "concurrent analysis" or "incidence study" or "incidence survey" or "incidence analysis" or "follow-up study" or "follow-up survey" or "follow-up analysis" or "observational study" or "observational survey" or "observational analysis" or "case study" or "case series" or "clinical series" or "case studies" or "clinical study" or "clinical trial" or "evaluation study" or "evaluation survey" or "evaluation analysis" or "twin study" or "twin survey" or "twin analysis" or "validation study" or "validation survey" or "validation analysis" or "experimental study" or "experimental analysis" or "field study" or "field survey" or "field analysis" or "in vivo study" or "in vivo analysis" or "panel study" or "panel survey" or "panel analysis" or "pilot study" or "pilot survey" or "pilot analysis" or "prevention study" or "prevention survey" or "prevention analysis" or "replication study" or "replication analysis" or "theoretical study" or "theoretical analysis" or "trend study" or "trend survey" or "trend analysis")
6 3 and (4 or 5)
7 PMID(0*) or PMID(1*) or PMID(2*) or PMID(3*) or PMID(4*) or PMID(5*) or PMID(6*) or PMID(7*) or PMID(8*) or PMID(9*)
8 6 and not 7
9 DOCTYPE(le) or DOCTYPE(ed) or DOCTYPE(bk) or DOCTYPE(er) or DOCTYPE(no) or DOCTYPE(sh)
10 8 and not 9

A systematic review and meta-analysis of off-loading methods for diabetic foot ulcers

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Background: **Increased plantar foot pressure is one of several key factors that lead to diabetic foot ulcers. Multiple methods have been proposed to relieve this pressure and thus enhance wound healing and potentially prevent relapse. We aimed in this systematic review to find the best available evidence for off-loading methods.**

Methods: **We searched MEDLINE, Embase, Cochrane CENTRAL, Web of Science, and Scopus through October 2011. Pairs of independent reviewers selected studies and extracted data. Predefined outcomes of interest included complete wound healing, time to complete wound healing, amputation, infection, and relapse rates.**

Results: **We identified 19 interventional studies, of which 13 were randomized controlled trials, including data from 1605 patients with diabetic foot ulcers using an off-loading method. The risk of bias in the included studies was moderate. This analysis demonstrated improved wound healing with total contact casting over removable cast walker, therapeutic shoes, and conventional therapy. There was no advantage of irremovable cast walkers over total contact casting. There was improved healing with half-shoe compared with conventional wound care. Therapeutic shoes and insoles reduced relapse rate in comparison with regular footwear. Data were sparse regarding other off-loading methods.**

Conclusions: **Although based on low-quality evidence (ie, evidence warranting lower certainty), benefits are demonstrated for use of total contact casting and irremovable cast walkers in the treatment of diabetic foot ulcers. Reduced relapse rate is demonstrated with various therapeutic shoes and insoles in comparison with regular footwear. (J Vasc Surg 2016;63:59S-68S.)**

The etiology of diabetic foot ulcer is multifactorial; peripheral neuropathy, foot deformity, and trauma are considered the most common factors that contribute to it.[1] Other risk factors include but are not limited to peripheral vascular disease, increasing duration of diabetes, past history of foot ulcers or amputation, peripheral edema, and increase in plantar foot pressure.[2] Around 50% of diabetic amputations are due to trauma caused by poorly fitting footwear.[3]

Interventions that relieve the pressure are proposed to enhance wound healing and potentially prevent the relapse of ulcers, thus preventing amputations.[4,5] Several methods are used for off-loading; the most efficient method among them is yet to be known.

Our aim was to conduct a systematic review to evaluate the quality of the evidence supporting the existing off-loading methods and to estimate the magnitude of benefit and relative efficacy of each one of them.

METHODS

This systematic review is protocol driven and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[6]

Eligibility criteria. Eligible studies were randomized trials and controlled observational studies that enrolled patients with diabetic foot ulcers treated by any off-loading method compared with a different one and reported the outcomes of interest. We were interested in studies that assess the impact of the intervention on patient-important outcomes, such as rate of complete wound healing, time to complete wound healing, amputation, hospitalization, relapse, and infection rates. Studies were included regardless of language, size, or duration of patient follow-up. We excluded articles that were not original studies like review articles, commentaries, and letters. We also excluded uncontrolled studies.

Study identification. The search strategy was designed and conducted by an experienced reference librarian (L.J.P.) with input from the study's principle investigator (M.H.M.). A comprehensive search of several databases from each database's earliest inclusive dates to

From the Evidence-based Practice Center,[a] Mayo Clinic Libraries,[f] and Division of Preventive, Occupational and Aerospace Medicine,[g] Mayo Clinic, Rochester; the Unidad de Conocimiento y Evidencia (CONEVID), Lima[b]; the Second Medical Department, Aristotle University Thessaloniki, Thessaloniki[c]; the Phoenix VA Health Care System, Phoenix[d]; and the Department of Internal Medicine, University of Missouri, Columbia.[e]

This review was partially funded by a contract from the Society for Vascular Surgery.

Author conflict of interest: none.

Additional material for this article may be found online at www.jvascsurg.org.

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Independent peer review and oversight have been provided by members of the Society for Vascular Surgery Document Oversight Committee: Peter Gloviczki, MD (Chair), Martin Bjorck, MD, Ruth Bush, MD, Thomas Forbes, MD, Michel Makaroun, MD, and Gregory Moneta, MD.

0741-5214

http://dx.doi.org/10.1016/j.jvs.2015.10.006

October 2011 was conducted. The databases included Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid Embase, Ovid Cochrane Database of Systematic Reviews, Ovid Cochrane Central Register of Controlled Trials, and Scopus. We identified additional candidate studies by review of bibliography of included articles and contact with experts. Controlled vocabulary supplemented with keywords was used to search for the topic: diabetic foot off-loading, limited to randomized and nonrandomized studies. The detailed search strategy is available in the Appendix (online only).

Data collection. All relevant abstracts were downloaded into an endnote library and uploaded into an online reference management system (DistillerSR). Reviewers working independently and in duplicate screened the abstracts for eligibility. Disagreements were automatically upgraded to the next level of screening. Full texts of eligible abstracts were retrieved and screened in duplicate. Disagreements at this level were resolved by discussion and consensus. We calculated the inter-reviewer agreement beyond chance (κ) during the full-text screening level. Using a standardized piloted web-based form, reviewers extracted descriptive, methodologic, and outcome data from all eligible studies.

For each study, we abstracted the following descriptive data: detailed description of baseline characteristics (eg, main demographic characteristics, type and duration of diabetes, size and duration of the ulcer) and interventions received (active or control) for all participants enrolled. We also extracted data for outcomes and assessment of methodologic quality. Extracted data were collated by a third independent reviewer, and inconsistencies were resolved by referring to the full-text article.

Methodologic quality and risk of bias assessment. Two reviewers independently assessed the quality of studies included. Nonrandomized studies were evaluated using the Newcastle-Ottawa scale[7]; we assessed outcome ascertainment, adjustment for confounders, proportion of patients lost to follow-up, and sample selection in each study. Randomized trials were evaluated using the Cochrane risk of bias assessment tool[8]; domains assessed included randomization, blinding, allocation concealment, baseline imbalances, loss to follow-up data, and bias due to funding. The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methods.[9,10] Following this approach, randomized trials are considered to warrant high-quality evidence (ie, high certainty), and observational studies warrant low-quality evidence. Then the evidence grading can be increased (if a large effect is observed) or decreased if other factors are noted, such as studies being at increased risk of bias or imprecise (small with wide confidence intervals [CIs]).

Statistical analysis. We pooled relative risk (RR) and 95% CI across included studies using random-effects meta-analysis described by DerSimonian and Laird.[11] For continuous outcomes, we pooled the weighted mean difference across studies. Between-studies heterogeneity was calculated by I^2 statistic, which estimates the proportion of variation in results across studies that is not due to chance.[12] Meta-analysis was completed using Comprehensive Meta-Analysis (CMA) version 2.2 (Biostat Inc, Englewood, NJ).

Subgroup analysis and publication bias. We did not perform any subgroup analyses because of the limited amount of studies that compared each intervention. Evaluation of publication bias was not feasible because of the small number of included studies per comparison.[13]

RESULTS

Search results and included studies

The literature search yielded 675 potentially relevant abstracts. We identified 19 interventional studies (13 randomized controlled trials [RCTs] and six controlled observational studies) including data from 1605 patients with diabetic foot ulcers treated with an off-loading method that fulfilled our inclusion criteria and were eligible for data extraction, of which 6 reported sufficient data for meta-analyses (Fig 1). The interventions described included total contact casting (TCC), instant total contact casting (iTCC) or irremovable cast walkers, removable cast walker (RCW), therapeutic shoes and insoles, felted foam, pneumatic walkers, and conventional dressing.

Studies in which irremovable casts were used excluded patients with ischemia. The definition of ischemia, however, varied across studies: absent foot pulse or a transcutaneous oxygen pressure ($TcPo_2$) <40 mm Hg[14,15]; ankle-brachial index (ABI) <0.6 or $TcPo_2$ <30 mm Hg[16,17]; ABI <0.9 or $TcPo_2$ <50 mm Hg[18]; absent dorsalis pedis and posterior tibial pulse[19]; ABI <0.9[20]; and clinically critical ischemia or wound with gangrene or necrosis or $TcPo_2$ <20 mm Hg or inability to detect with Doppler a major leg artery or based on angiography.[21]

The characteristics of included studies are described in Table I. The adjusted agreement between reviewers (κ) averaged 0.80 as calculated by the online system.

Methodologic quality and risk of bias

The quality of the included studies ranges from low to moderate. Randomization and allocation concealment were adequately described in only six and four of 13 RCTs, respectively. Blinding was described in only one study, which reported that outcome assessors and data collectors were blinded. Lack of blinding is unlikely to introduce bias for objective outcomes like amputation; however, it could introduce significant bias for subjective or assessor-dependent outcomes, such as complete wound healing. No baseline imbalances were mentioned in any of the studies. The percentage lost to follow-up ranged from 0% to 17%, with five studies reporting no losses.

The overall methodologic quality of observational studies was moderate. The selection of cohorts of patients was well described in 50% of the studies. Such studies

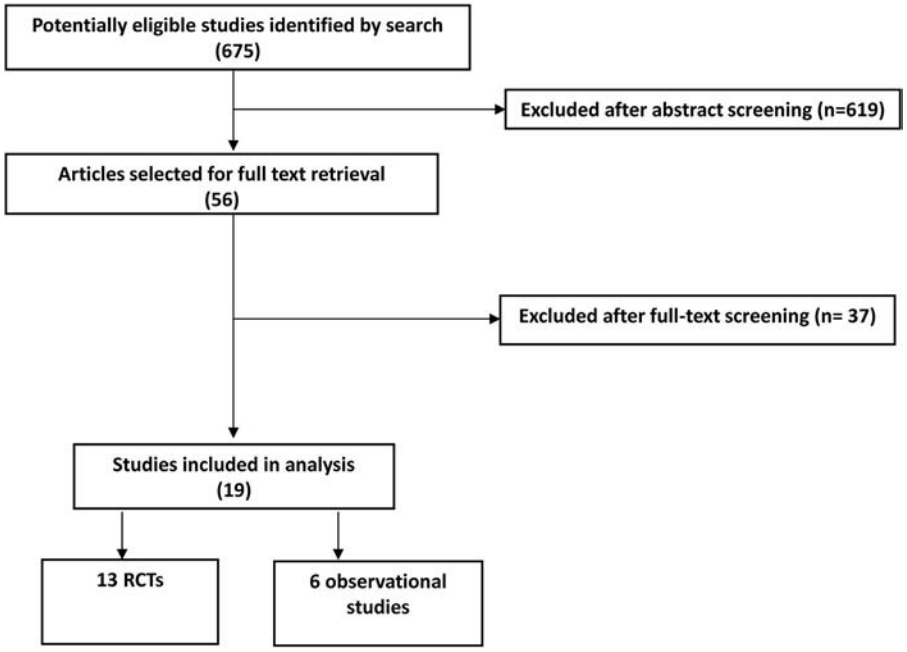

Fig 1. Flow diagram of how studies were screened and selected. *RCTs,* Randomized controlled trials.

appeared to report on consecutive samples of patients. Thus, selection bias is possible in other studies with inadequate reporting. Moreover, follow-up was adequate, and four studies reported a 100% response rate. Only one of them adjusted for potential confounders. Tables II and III describe the quality of included studies.

Meta-analysis

TCC vs RCW. On the basis of three RCTs,[15,18,21] there was a nonsignificant improvement in healing rate with TCC compared with RCW (RR, 1.15; 95% CI, 0.92-1.45; $I^2 = 0.00\%$; Fig 2), with a significant reduction in mean time to complete wound healing for the TCC group (weighted mean difference, −12.36 days; 95% CI, −22.63 to −2.09; $P = .018$; $I^2 = 91.36\%$; Fig 3). Quality of evidence is low, downgraded because of methodologic limitations of the included studies, heterogeneity, and imprecision (wide CIs due to small number of patients).

TCC vs conventional wound therapy. Pooling of one RCT[25] and one controlled cohort[26] revealed a nonsignificant improvement in healing rate with TCC compared with conventional wound therapy (RR, 1.76; 95% CI, 0.77-4.02; $P = .184$; Fig 4). Quality of evidence is low because of methodologic limitations of the included studies and imprecision (wide CIs due to small number of patients).

Relapse: Therapeutic shoes and insoles vs regular footwear. A meta-analysis of two RCTs[3,28] and two controlled cohorts[23,30] showed that therapeutic shoes and insoles significantly reduce ulcer relapse rate compared with regular footwear (RR, 0.34; 95% CI, 0.15-0.79; $P = .012$; $I^2 = 85.17\%$; Fig 5). Quality of evidence is low because of methodologic limitations, imprecision (wide CIs due to small number of patients), and significant heterogeneity in the results.

Other comparisons (reported in individual studies)

Ha Van et al[21] reported a statistically nonsignificant difference in healing rate with nonremovable fiberglass cast boots compared with half-shoe (RR, 1.15; 95% CI, 0.91-1.44; $P = .24$). However, secondary osteomyelitis was significantly reduced in the cast group compared with the off-loading shoe group (RR, 0.28; 95% CI, 0.08-0.92; $P = .035$). Osteomyelitis was subjectively defined in this study as a palpable bone in an inflammatory ulcer, radiographic evidence of bone erosions, or joint involvement deep to the ulcer. Quality of evidence is low because of methodologic limitations of the study.

A controlled cohort by Birke et al[22] compared TCC with alternative off-loading methods (an accommodative dressing, a healing shoe, or a walking splint) and reported no difference between healing time in any of the three comparisons, after adjusting for ulcer grade (1, 2, or 3) and width in a stepwise lognormal regression model. Quality of evidence is low because of methodologic limitations of the study.

One RCT[16] compared the healing rate for TCC (fiberglass cast) vs special therapeutic shoe and reported an increased healing rate in favor of TCC (RR, 2.40; 95% CI, 1.01-5.73; $P = .048$). Quality of evidence is low because of methodologic limitations of the study.

One RCT compared irremovable cast walkers (iTCC) with RCW.[14] Investigators constructed iTCC by modifying the RCW (by wrapping the traditional RCW in a layer of

Table I. Characteristics of included studies

Study	*Country*	*Care setting*	*No.*	*Age, years, mean*	*Male, %*
Armstrong,[15] 2001	United States	NR	63	NR	82.5
Armstrong,[14] 2005	United States	NR	50	65.6	88
Birke,[22] 2002	United States	Louisiana State University Health Sciences Center Diabetes Foot Program	70	56	54
Busch,[23] 2003	Germany	Large practice of two internists specializing in diabetology	92	63	53
Caravaggi,[16] 2000	Italy	NR	50	60	68
Caravaggi,[17] 2007	Italy	Diabetic Foot Department, University Hospital	60	NR	NR
Chantelau,[24] 1993	Germany	University Outpatient Diabetes Foot Clinic	48	57	73
Faglia,[18] 2010	Italy	Two centers specializing in diabetic foot management	48	60.3	66.7
Ganguly,[25] 2008	India	NR	58	<20 to >70	67.3
Ha Van,[21] 2003	France	Diabetic foot clinic in a teaching hospital	93	60	88.5
Katz,[19] 2005	United States	Referral clinic dedicated to the treatment of diabetic foot disorders	41	50.9	68
Mueller,[26] 1989	United States	Diabetic Foot Center and Physical Therapy Department at Washington University School of Medicine	40	55	70
Nube,[27] 2006	Australia	Foot clinic	38	57	80-85
Piaggesi,[20] 2007	Italy	Section of Diabetes and Metabolic Diseases, Department of Endocrinology and Metabolism, University Hospital	40	60.4	NR
Reiber,[3] 2002	United States	Two Washington State health care organizations	400	62	77
Uccioli,[28] 1995	Italy	Two teaching hospitals	69	60	62.3
Van De Weg,[29] 2008	Netherlands	Rehabilitation department from two hospitals	43	62	78.5
Viswanathan,[30] 2004	India	NR	241	56	64.73
Zimny,[31] 2002	Germany	NR	61	61	54

HbA_{1c}, Hemoglobin A_{1c}; *iTCC,* instant total contact casting; *NA,* not applicable; *NR,* not reported; *RCW,* removable cast walker; *TCC,* total contact casting; *TDT,* traditional dressing treatment.

Table I. Continued.

Patient characteristics	*Intervention 1*	*Intervention 2*	*Ulcer area, cm²*	*Follow-up, months*
Diabetes duration: 17 years Ulcer duration: 5.2 months All patients had clinically significant loss of protective sensation	TCC	RCW	1.3	3
HbA_{1c}: 8.2%	iTCC	RCW	2.3 ± 1.2	3 or until wound healing
TCC Wagner grade: 2.2 Ulcer duration: 184 days Healing shoe Wagner grade: 1.7 Ulcer duration: 68 days	TCC	Alternative off-loading methods: an accommodative dressing (26 patients), a healing shoe (57 patients), a walking splint (18 patients)	Mean, 1.05	3
Diabetes duration: 13 years Type 1: 8.7% Type 2: 91.3%	Customized stock diabetic shoes	Regular shoes	NA	14.1
Diabetes duration: 17 years	Fiberglass cast	Diabetic shoe	5.1	1
NR	Fiberglass off-loading cast	Aircast pneumatic walker	Walker: 3.4 ± 3.0 Fiberglass: 3.9 ± 3.4	3
Diabetes duration: 17 years 12 patients had prior amputations	Standard treatment + half-shoe	Standard treatment	NR	NR
TCC group Diabetes duration: 18 years HbA_{1c}: 9.1% Stabil-D group Diabetes duration: 17 years HbA_{1c}: 7.5% Half of the patients had previous minor amputations	Nonremovable fiberglass off-bearing cast (TCC group)	Walker cast (Stabil-D group)	TCC: 1.4 ±1.2 Stabil-D: 2.2 ± 2.3	3
NR	TCC	Simple dressing	NR	6
Type 1: 19.3% Type 2: 80.7% Diabetes duration: 17 years Ulcer duration: 264.5 days 14.5% of patients had the ulcers for >6 months	Cast boot	Off-loading shoe	Cast boot: 2.8 Off-loading shoe: 1.6	NR
92.5% of patients had type 2 diabetes Diabetes duration: 14 years Ulcer duration: 216 days	RCW with single layer of fiberglass casting material (iTCC)	Standard TCC	iTCC: 3.1 cm^2 TCC: 2.9 cm^2	3
Type 1: 28% Type 2: 72% Diabetes duration: 17 years Ulcer duration: 160 days	TCC	TDT	TCC: 1.8 ± 2.5 TDT: 2.8 ± 3.5	3
Diabetes duration: 13 years HbA_{1c}: 9.5% Ulcer duration: 240 days	Felt deflective padding on the skin	Felt deflective padding in the shoe	0.5	1
Diabetes duration: 15.5 years HbA_{1c}: 7.7%	TCC	Optima Diab walker	A: 3.7 ± 1.6 B: 3.9 ± 1.8	3
33% of patients had diabetes >6 years, 11% for 6-24 years, 56% > 25 years (type 1: 7%; type 2: 93%) 58% of participants were insensate to monofilament 32% had a moderate foot deformity	Therapeutic shoes with inserts	Usual footwear	NA	24
Type 2: 75% Diabetes duration: 17 years	Therapeutic shoes	Nontherapeutic shoes	NA	12
Diabetes duration: 12 years Ulcer duration: 3-8 weeks	TCC	Custom-made temporary foot wear	TCC: 4.2 ± 3.1 Shoe: 3.0 ± 3.1 (All the patients but two had grade 2 ulcers)	4
Diabetes duration: 12.3 years	Therapeutic footwear with different types of insoles: microcellular rubber (100 patients), polyurethane (59 patients), and molded insole (32 patients)	Regular footwear with leather board insoles	NA	NR
Type 1: 36% Type 2: 64% Diabetes duration: 20 years	Felted foam	Conventional therapy	Felted foam: 1.1 cm^2 Conventional therapy: 1.19 cm^2	1-14

Table II. Risk of bias indicators in randomized trials

Study	*Randomization list prepared in advance*	*Allocation concealment*	*Blinding*	*Baseline imbalances*	*Follow-up*	*Adherence to treatment*	*Lost to follow-up, %*	*Funding*
Armstrong,[15] 2001	Computerized randomization schedule	NR	NA/NR	No	Yes, regular clinic visits	NR	0	Not-for-profit sources
Armstrong,[14] 2005	Computerized randomization schedule	Yes; method not reported	NA/NR	No	Yes, regular clinic visits	NR	8	Not-for-profit sources
Caravaggi,[16] 2000	A table of random numbers	Assigned by phone	NA/NR	No	Yes, regular clinic visits	NR	0	NR
Caravaggi,[17] 2007	NR	NR	NA/NR	No	Yes, regular clinic visits	Yes	3	NR
Faglia,[18] 2010	NR	Randomization code break envelopes	NA/NR	No	Yes, regular clinic visits	NR	6.25	Includes for-profit source
Ganguly,[25] 2008	NR	NR	NA/NR	No	Yes, regular clinic visits	NR	5	NR
Katz,[19] 2005	Random number table	NR	NA/NR	No	Yes, regular clinic visits	NR	17	Includes for-profit source
Piaggesi,[20] 2007	NR	NR	NA/NR	No	Yes, regular clinic visits	NR	0	Includes for-profit source
Reiber,[3] 2002	NR	NR	NA/NR	No	Yes, regular clinic visits	Patients reported time they used the shoe	13.7	Not-for-profit sources
Uccioli,[28] 1995	NR	NR	NA/NR	No	Yes, regular clinic visits	NR	0	Includes for-profit source
Nube,[27] 2006	Drawing lots	NR	NA/NR	No	Yes, regular clinic visits	NR	15.7	Not-for-profit sources
Van De Weg,[29] 2008	Randomization list prepared in advance	Opaque sealed envelopes	Yes; outcome assessors, data collectors	No	Yes, patients were evaluated at weeks 2, 4, 8, and 16	NR	11.63	Not-for-profit sources
Zimny,[31] 2002	NR	NR	NA/NR	No	Yes, regular clinic visits	NR	0	NR

NA, Not applicable; *NR*, not reported.

cohesive or plaster bandage). They reported an increased healing rate for the iTCC group compared with RCW (RR, 1.59; 95% CI, 1.06-2.40; $P = .027$). Moreover, there was a shorter healing time for patients treated with iTCC (41.6 ± 18.7 vs 58.0 ± 15.2 days; $P = .02$).[14] Quality of evidence is low because of methodologic limitations of the studies and imprecision (wide CIs due to small number of patients).

One RCT by Katz et al[19] compared iTCC with standard TCC and reported no difference in the rate of complete healing between the two groups (RR, 1.12; 95% CI, 0.79-1.59; $P = .523$). Also, there was no difference in amputation rate (RR, 1.05; 95% CI, 0.07-15.68; $P = .971$). Quality of evidence is low because of methodologic limitations of the study.

One RCT[31] comparing felted foam vs conventional wound therapy reported no statistically significant difference in the time to complete healing between the two groups (mean of 79.6 vs 83.2 days; $P = .61$). Quality of evidence is low because of methodologic limitations of the study.

One observational study by Chantelau et al[24] evaluated the effect of half-shoe compared with conventional wound care and reported that the number of patients who achieved complete healing was significantly higher in the half-shoe group (RR, 1.63; 95% CI, 1.14-2.32; $P = .007$). They also reported significant reduction in the hospitalization rate for the half-shoe group compared with the conventional therapy group (RR, 0.09; 95% CI, 0.01-0.69; $P = .020$). Quality of evidence is low because of methodologic limitations of the study.

One RCT[17] compared a pneumatic off-loading device with a fiberglass off-loading cast and reported no statistical difference in the healing rates between the two groups (RR, 1.04; 95% CI, 0.81-1.34; $P = .738$). However, they reported that the Kaplan-Meier curves showed a healing rate of 59.9% per month in the pneumatic device group vs 40.89% in the fiberglass cast group ($P < .005$), with an average healing

Table III. Methodologic quality of included observational studies

Study	*Representativeness*	*Did the groups come from the same community?*	*Was exposure properly verified?*	*Adjustment for confounders*	*Outcome assessment*	*Sufficient follow-up*	*Similarity of outcome assessment*	*Response rate*	*Funding*
Birke,[22] 2002	Truly representative	Yes	Yes	No	Yes, similar	Yes	Yes	Response rate: 100%	NR
Busch,[23] 2003	Truly representative	Yes	Yes	No	Yes, similar	Yes	Yes	Response rate: 100%	Includes for-profit source
Chantelau,[24] 1993	NR	Yes	Yes	Yes, they adjusted for sex, age, duration of diabetes, ulcer grading	Yes, similar	NR	Yes	NR	NR
Ha Van,[21] 2003	Truly representative	Yes	Yes	No	Yes, similar	NR	Yes	Response rate: 100%	NR
Mueller,[26] 1989	NR	Yes	Yes	No	Yes, similar	Yes	Yes	NR	Only not-for-profit source
Viswanathan,[30] 2004	NR	Yes	Yes	No	Yes, similar	NR	Yes	Response rate: 100%	NR

NR, Not reported.

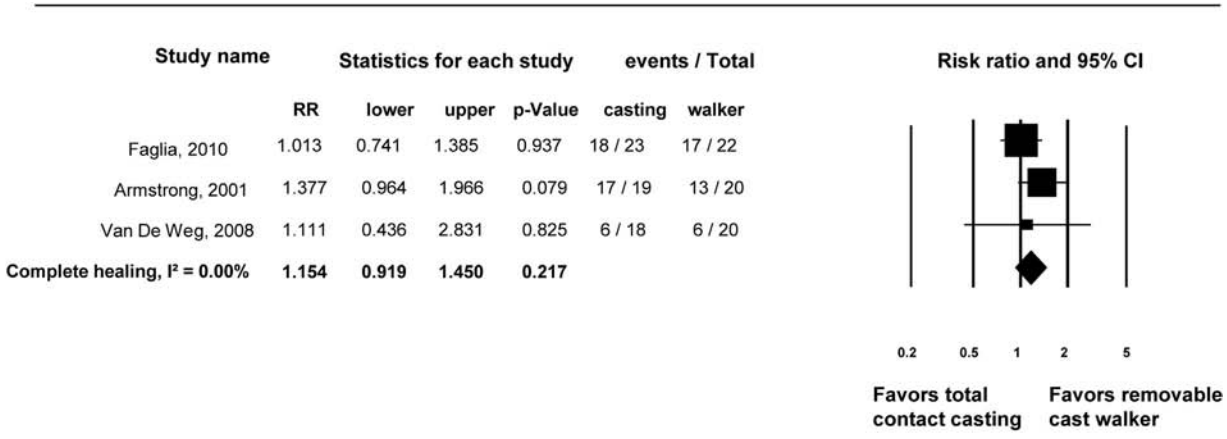

Fig 2. Total contact casting (TCC) vs removable cast walker (RCW), complete healing. *CI,* Confidence interval; *RR,* relative risk.

time of 71 days in the pneumatic device group and 48 days in the fiberglass cast group. Quality of evidence is low because of methodologic limitations of the study.

One RCT by Nube et al[27] compared the application of felt deflective padding on the skin with its application in the shoe and reported that similar healing rates were achieved in both groups ($P = .9$). Further analysis was not possible because the number of patients who achieved complete healing was not reported separately for the two groups. Quality of evidence is low because of methodologic limitations of the study.

DISCUSSION

We conducted a systematic review and meta-analyses to evaluate the comparative effectiveness of different offloading methods for diabetic foot ulcers. This study demonstrated some advantages for TCC over RCW, therapeutic shoes, and conventional therapy. There was no advantage for iTCC over TCC. Irremovable casts were used in the studies in patients without ischemia. There was improved healing with half-shoe compared with conventional footwear. This study also showed that therapeutic shoes and insoles provided a clear benefit in preventing

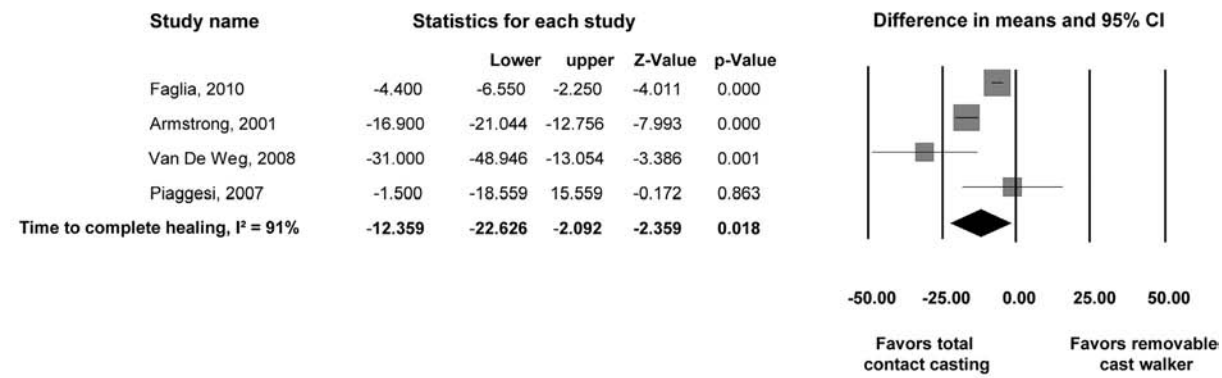

Fig 3. Total contact casting (TCC) vs removable cast walker (RCW), time to heal in days. *CI,* Confidence interval.

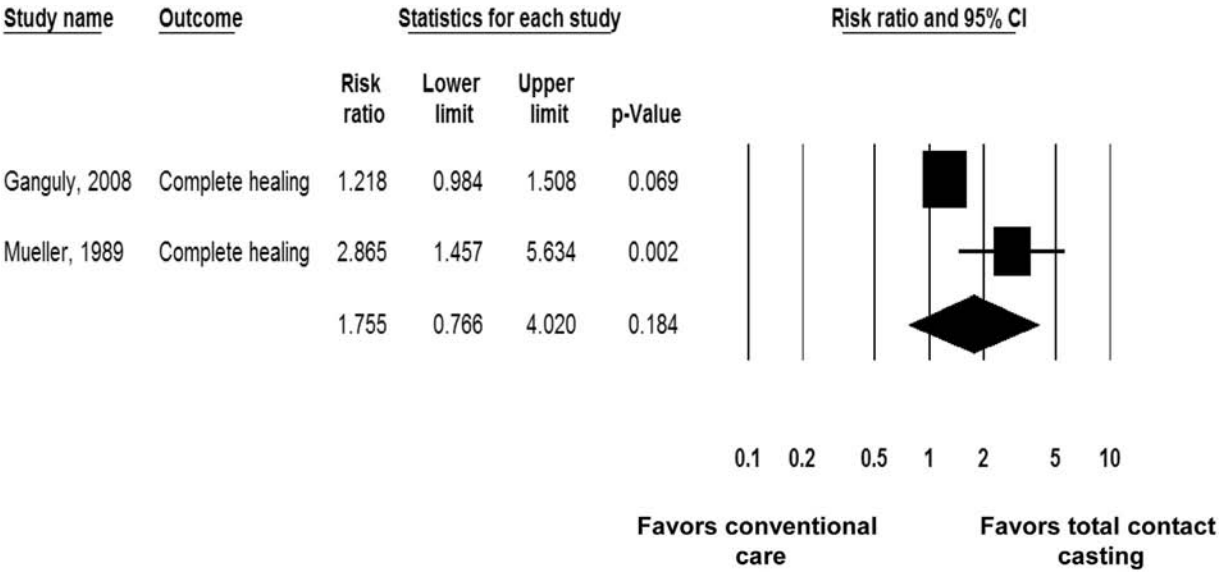

Fig 4. Total contact casting (TCC) vs conventional wound care, complete healing. *CI,* Confidence interval.

relapse in comparison with regular footwear. Data were sparse regarding other off-loading methods.

The quality of comparative effectiveness evidence (ie, the confidence in the estimates) is low, considering the methodologic limitations of the included studies and imprecision (the small sample size and wide CIs). Therefore, future studies may demonstrate different results, particularly if their inclusion criteria are different. In addition, the available data do not allow control for risk factors and other important variables (smoking, ABI, toe-brachial index, diabetes control, renal function, wound depth and area, and vascular supply status), and therefore the association between off-loading method and the outcomes could be confounded in the observational studies and in randomized trials with small size.

Our results are consistent with earlier evidence synthesis attempts. Cavanagh and Bus[32] demonstrated the benefit of TCC and irremovable walker devices; nevertheless, they did not attempt meta-analysis. Paton et al[33] conducted a systematic review that suggested some benefit of insoles in preventing diabetic ulcers. Maciejewski et al[4] described the effect of therapeutic footwear in preventing reulceration. Bus et al[34] and Spencer[5] both highlighted that the evidence supporting the use of the off-loading methods is weak and that further studies need to be conducted, which is consistent with our findings. Our review updated the evidence base and expanded on the previous findings by incorporating any off-loading method.

The accompanying guideline by the Society for Vascular Surgery will elaborate more on these options

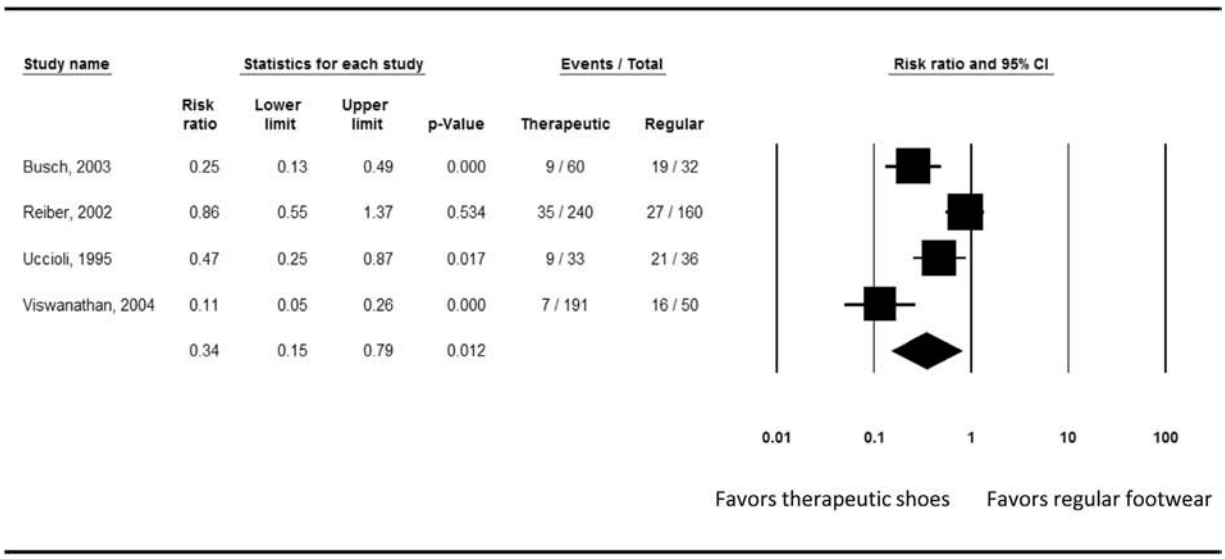

Fig 5. Therapeutic shoes and insoles vs regular footwear, relapse. *CI,* Confidence interval.

and discuss the clinical and practical implications so that both the physician and the patient can select the most favorable method according to the specific clinical scenario, patients' values and preferences, and available resources.

CONCLUSIONS

Although based on low-quality evidence (ie, evidence warranting lower certainty), benefits are demonstrated for use of TCC and irremovable cast walkers in the treatment of diabetic foot ulcers. Reduced relapse rate is demonstrated with various therapeutic shoes and insoles in comparison with regular footwear.

AUTHOR CONTRIBUTIONS

Conception and design: TE, GP, JD, AT, MN, RF, BF, RH, LP, MM
Analysis and interpretation: TE, MM
Data collection: TE, GP, JD, AT, MN, RF, BF, RH, LP, MM
Writing the article: TE, GP, JD, AT, MN, RF, BF, RH, LP, MM
Critical revision of the article: TE, GP, JD, AT, MN, RF, BF, RH, LP, MM
Final approval of the article: TE, GP, JD, AT, MN, RF, BF, RH, LP, MM
Statistical analysis: MM
Obtained funding: MM
Overall responsibility: MM

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Submitted Sep 8, 2015; accepted Oct 8, 2015.

Additional material for this article may be found online at www.jvascsurg.org.

APPENDIX (online only).

Actual search strategy

Ovid. Databases: Embase 1988 to 2011 Week 40, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present, EBM Reviews—Cochrane Central Register of Controlled Trials 4th Quarter 2011, EBM Reviews—Cochrane Database of Systematic Reviews 2005 to October 2011.

Search strategy:

#	*Searches*	*Results*
1	((diabetic or diabetes) adj3 (foot or feet)).mp.	14923
2	exp Diabetic Foot/	11805
3	1 or 2	14923
4	exp Casts, Surgical/	11992
5	(cast or casting or casts).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	69473
6	exp walking aid/	2629
7	exp Walkers/	3062
8	(offload* or "off-load*").mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	1152
9	walker*.ti.	4174
10	exp Orthotic Devices/	11121
11	exp shoe/	8612
12	(shoe or shoes).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	14229
13	(sandal or sandals).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	314
14	(non-weightbearing or nonweightbearing).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	515
15	"nonweight bearing".mp.	394
16	"non-weight bearing".mp.	1902
17	insole*.mp.	1617
18	or/4-17	102447
19	3 and 18	1858
20	exp controlled study/	3639965
21	exp evidence based medicine/	518676
22	evidence-based.mp.	175991
23	((control$ or randomized) adj2 (study or studies or trial or trials)).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	4669099
24	meta analysis/	87758
25	meta-analys$.mp.	139569
26	exp "systematic review"/	44105
27	systematic review$.mp.	98690
28	exp Guideline/ or exp Practice Guideline/	271941
29	guideline$.ti.	87215
30	or/20-29	5188997
31	exp case study/	1572995
32	exp Cohort Studies/	1330764
33	exp longitudinal study/	880349
34	exp retrospective study/	628418
35	exp prospective study/	532053
36	exp observational study/	23108
37	exp comparative study/	2198791
38	exp clinical trial/	1477518
39	exp evaluation/	1088304
40	exp twins/	39276
41	exp validation study/	28010
42	exp experimental study/ or exp field study/ or exp in vivo study/ or exp panel study/ or exp pilot study/ or exp prevention study/ or exp quasi experimental study/ or exp replication study/ or exp theoretical study/ or exp trend study/	6878167
43	((clinical or evaluation or twin or validation or experimental or field or "in vivo" or panel or pilot or prevention or replication or theoretical or trend or comparative or cohort or longitudinal or retrospective or prospective or population or concurrent or incidence or follow-up or observational) adj (study or studies or survey or surveys or analysis or analyses or trial or trials)).mp.	6826285
44	("case study" or "case series" or "clinical series" or "case studies").mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	154865

(*Continued on next page*)

Continued.

#	*Searches*	*Results*
45	or/31-44	12888282
46	19 and (30 or 45)	1016
47	from 19 keep 957-1756	800
48	limit 47 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or twin study) [Limit not valid in Embase,CDSR; records were retained]	170
49	46 or 48	1016
50	limit 49 to (book or book series or editorial or erratum or letter or note or addresses or autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	34
51	49 not 50	982
52	from 19 keep 1757-1858	102
53	51 or 52	1029
54	remove duplicates from 53	654

Scopus

1 TITLE-ABS-KEY((diabetes w/3 foot) or (diabetic w/3 foot) or (diabetes w/3 feet) or (diabetic w/3 feet))

2 TITLE-ABS-KEY(cast or casts or casting or off-load* or "off-load*" or orthotic* or shoe* or sandal* or "non-weightbearing" or nonweight-bearing or "nonweight bearing" or "non-weight bearing" or insole*)

3 TITLE(walker or walkers)

4 TITLE-ABS-KEY((evidence W/1 based) OR (meta W/1 analys*) OR (systematic* W/2 review*) OR guideline OR (control* W/2 stud*) OR (control* W/2 trial*) OR (randomized W/2 stud*) OR (randomized W/2 trial*))

5 TITLE-ABS-KEY("comparative study" OR "comparative survey" OR "comparative analysis" OR "cohort study" OR "cohort survey" OR "cohort analysis" OR "longitudinal study" OR "longitudinal survey" OR "longitudinal analysis" OR "retrospective study" OR "retrospective survey" or "retrospective analysis" OR "prospective study" OR "prospective survey" OR "prospective analysis" OR "population study" OR "population survey" OR "population analysis" OR "concurrent study" OR "concurrent survey" OR "concurrent analysis" or "incidence study" OR "incidence survey" OR "incidence analysis" OR "follow-up study" OR "follow-up survey" OR "follow-up analysis" or "observational study" OR "observational survey" OR "observational analysis" OR "case study" OR "case series" OR "clinical series" OR "case studies" or "clinical study" OR "clinical trial" or "evaluation study" OR "evaluation survey" OR "evaluation analysis" or "twin study" OR "twin survey" OR "twin analysis" or "validation study" OR "validation survey" OR "validation analysis" or "experimental study" OR "experimental analysis" or "field study" OR "field survey" OR "field analysis" or "in vivo study" OR "in vivo analysis" or "panel study" OR "panel survey" OR "panel analysis" or "pilot study" OR "pilot survey" OR "pilot analysis" or "prevention study" OR "prevention survey" OR "prevention analysis" or "replication study" OR "replication analysis" or "theoretical study" OR "theoretical analysis" or "trend study" OR "trend survey" OR "trend analysis")

6 1 and (2 or 3) and (4 or 5)

7 PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)

8 6 and not 7

9 DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)

10 8 and not 9

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