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

Anil Hingorani, MD,[a] Glenn M. LaMuraglia, MD,[b] Peter Henke, MD,[c] Mark H. Meissner, MD,[d] Lorraine Loretz, DPM, MSN, NP,[e] Kathya M. Zinszer, DPM, MPH, FAPWCA,[f] Vickie R. Driver, DPM, MS, FACFAS,[g] Robert Frykberg, DPM, MPH, MAPWCA,[h] Teresa L. Carman, MD, FSVM,[i] William Marston, MD,[j] Joseph L. Mills Sr, MD,[k] and **Mohammad Hassan Murad, MD, MPH,[l]** *Brooklyn, NY; Boston and Worcester, Mass; Ann Arbor, Mich; Seattle, Wash; Danville, Pa; Providence, RI; Phoenix Ariz; Cleveland, Ohio; Chapel Hill, NC; Houston, Tex; and Rochester, Minn*

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

From the NYU Lutheran Medical Center, Brooklyn[a]; the Massachusetts General Hospital and Harvard Medical School, Boston[b]; the University of Michigan, Ann Arbor[c]; the University of Washington, Seattle[d]; the UMass Memorial, Worcester[e]; the Geisinger Health System, Danville[f]; the Brown University, Alpert Medical School, Providence[g]; the Carl T. Hayden Veterans Affairs Medical Center, Phoenix[h]; the University Hospitals Case Medical Center, Cleveland[i]; the University of North Carolina School of Medicine, Chapel Hill[j]; the Baylor College of Medicine in Houston, Houston[k]; and the Mayo Clinic, Rochester.[l]

Author conflict of interest: none.

Correspondence: Anil Hingorani, MD, NYU Lutheran Medical Center, 150 55th St, Brooklyn, NY 11220 (e-mail: ahingorani67@gmail.com).

Independent peer review and oversight have been provided by members of the Society for Vascular Surgery Document Oversight Committee: Peter Gloviczki, MD (Chair), Michael Conte, MD, Mark Eskandari, MD, Thomas Forbes, MD, Michel Makaroun, MD, Greg Moneta, MD, Russell Samson, MD, Timur Sarac, MD, Piergiorgio Settembrini, MD, and Thomas Wakefield, MD.

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

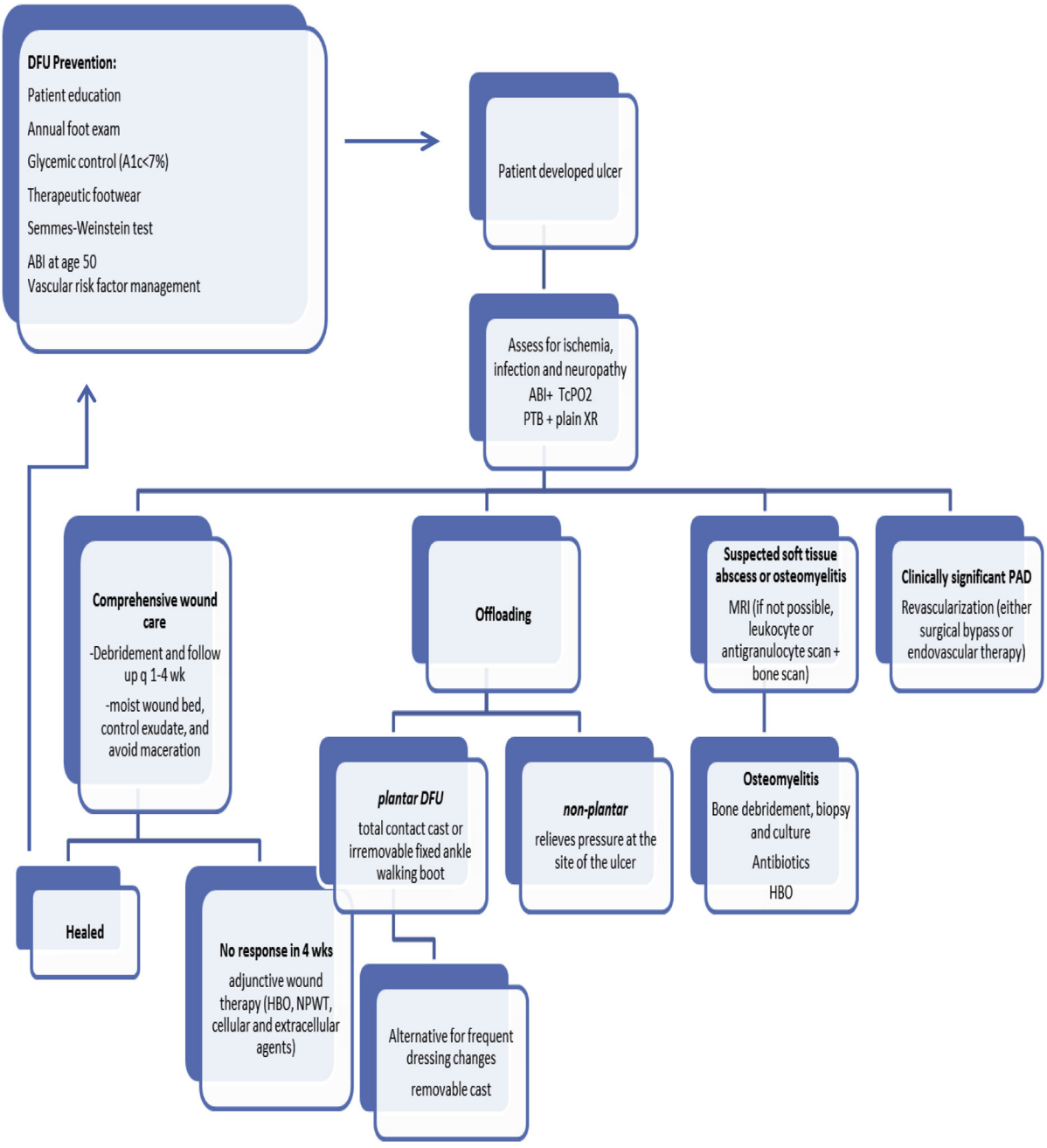

Fig. Algorithm for prevention and care of diabetic foot. *ABI,* Ankle-brachial index; *DFU,* diabetic foot ulcer; *HBO,* hyperbaric oxygen; *MRI,* magnetic resonance imaging; *NPWT,* negative pressure wound therapy; *PAD,* peripheral arterial disease; *PTB,* probe to bone; *$TcPo_2$,* transcutaneous 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
Analysis and interpretation: AH, GL, PH, MM, LL, KZ, VD, RF, TC, WM
Data collection: AH, GL, PH, MM, LL, KZ, VD, RF, WM
Writing the article: AH, GL, PH, MM, LL, KZ, VD, RF, TC, WM
Critical revision of the article: AH, GL, PH, MM, LL, KZ, VD, RF, TC, WM
Final approval of the article: AH, GL, PH, MM, LL, KZ, VD, RF, TC, WM
Statistical analysis: Not applicable
Obtained funding: Not applicable
Overall responsibility: AH

REFERENCES

1. IDF diabetes atlas, 6th edition. Available at: http://www.idf.org/diabetesatlas. Accessed November 13, 2015.
2. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3:e442.
3. Global status report on noncommunicable diseases 2010. Geneva: World Health Organization; 2011.
4. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet 2005;366:1719-24.
5. Boulton AJ. The diabetic foot: from art to science. The 18th Camillo Golgi lecture. Diabetologia 2004;47:1343-53.
6. Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. Diabetologia 2008;51:747-55.
7. Jeffcoate WJ, Chipchase SY, Ince P, Game FL. Assessing the outcome of the management of diabetic foot ulcers using ulcer-related and person-related measures. Diabetes Care 2006;29:1784-7.
8. Age-adjusted hospital discharge rates for nontraumatic lower extremity amputation (LEA) per 1,000 diabetic population, by level of amputation, United States, 1993–2009. Atlanta, Ga: Centers for Disease Control and Prevention (CDC), National Center for Health Statistics, Division of Health Interview Statistics; 2012.
9. Frykberg RG, Zgonis T, Armstrong DG, Driver VR, Giurini JM, Kravitz SR, et al. Diabetic foot disorders. A clinical practice guideline (2006 revision). J Foot Ankle Surg 2006;45(Suppl):S1-66.
10. Ortegon MM, Redekop WK, Niessen LW. Cost-effectiveness of prevention and treatment of the diabetic foot: a Markov analysis. Diabetes Care 2004;27:901-7.
11. Nabuurs-Franssen MH, Huijberts MS, Nieuwenhuijzen Kruseman AC, Willems J, Schaper NC. Health-related quality of life of diabetic foot ulcer patients and their caregivers. Diabetologia 2005;48:1906-10.
12. Prompers L, Huijberts M, Schaper N, Apelqvist J, Bakker K, Edmonds M, et al. Resource utilisation and costs associated with the treatment of diabetic foot ulcers. Prospective data from the Eurodiale Study. Diabetologia 2008;51:1826-34.
13. van Houtum WH. Barriers to the delivery of diabetic foot care. Lancet 2005;366:1678-9.
14. Institute of Medicine. Committee on standards for developing trustworthy clinical practice guidelines. Clinical practice guidelines we can trust. Washington, D.C.: The National Academies Press; 2011.
15. Murad MH, Montori VM, Sidawy AN, Ascher E, Meissner MH, Chaikof EL, et al. Guideline methodology of the Society for Vascular Surgery including the experience with the GRADE framework. J Vasc Surg 2011;53:1375-80.
16. Murad MH, Swiglo BA, Sidawy AN, Ascher E, Montori VM. Methodology for clinical practice guidelines for the management of arteriovenous access. J Vasc Surg 2008;48(Suppl):26S-30S.
17. American Diabetes Association. Peripheral arterial disease in people with diabetes. Diabetes Care 2003;26:3333-41.
18. Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012;54:e132-73.

19. Mayfield JA, Sugarman JR. The use of the Semmes-Weinstein monofilament and other threshold tests for preventing foot ulceration and amputation in persons with diabetes. J Fam Pract 2000;49(Suppl):S17-29.
20. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA 2005;293:217-28.
21. McCabe CJ, Stevenson RC, Dolan AM. Evaluation of a diabetic foot screening and protection programme. Diabet Med 1998;15:80-4.
22. Donohoe ME, Fletton JA, Hook A, Powell R, Robinson I, Stead JW, et al. Improving foot care for people with diabetes mellitus—a randomized controlled trial of an integrated care approach. Diabet Med 2000;17:581-7.
23. Reiber GE, Smith DG, Wallace C, Sullivan K, Hayes S, Vath C, et al. Effect of therapeutic footwear on foot reulceration in patients with diabetes: a randomized controlled trial. JAMA 2002;287:2552-8.
24. Litzelman DK, Slemenda CW, Langefeld CD, Hays LM, Welch MA, Bild DE, et al. Reduction of lower extremity clinical abnormalities in patients with non-insulin-dependent diabetes mellitus. A randomized, controlled trial. Ann Intern Med 1993;119:36-41.
25. Dargis V, Pantelejeva O, Jonushaite A, Vileikyte L, Boulton AJ. Benefits of a multidisciplinary approach in the management of recurrent diabetic foot ulceration in Lithuania: a prospective study. Diabetes Care 1999;22:1428-31.
26. Vedhara K, Beattie A, Metcalfe C, Roche S, Weinman J, Cullum N, et al. Development and preliminary evaluation of a psychosocial intervention for modifying psychosocial risk factors associated with foot re-ulceration in diabetes. Behav Res Ther 2012;50:323-32.
27. Mueller MJ, Tuttle LJ, Lemaster JW, Strube MJ, McGill JB, Hastings MK, et al. Weight-bearing versus nonweight-bearing exercise for persons with diabetes and peripheral neuropathy: a randomized controlled trial. Arch Phys Med Rehabil 2013;94:829-38.
28. Burns J, Wegener C, Begg L, Vicaretti M, Fletcher J. Randomized trial of custom orthoses and footwear on foot pain and plantar pressure in diabetic peripheral arterial disease. Diabet Med 2009;26:893-9.
29. Uccioli L, Faglia E, Monticone G, Favales F, Durola L, Aldeghi A, et al. Manufactured shoes in the prevention of diabetic foot ulcers. Diabetes Care 1995;18:1376-8.
30. Reiber GE, Smith DG, Wallace CM, Vath CA, Sullivan K, Hayes S, et al. Footwear used by individuals with diabetes and a history of foot ulcer. J Rehabil Res Dev 2002;39:615-22.
31. Tovey FI. The manufacture of diabetic footwear. Diabet Med 1984;1:69-71.
32. Spencer S. Pressure relieving interventions for preventing and treating diabetic foot ulcers. Cochrane Database Syst Rev 2000;(3):CD002302.
33. Waaijman R, Arts ML, Haspels R, Busch-Westbroek TE, Nollet F, Bus SA. Pressure-reduction and preservation in custom-made footwear of patients with diabetes and a history of plantar ulceration. Diabet Med 2012;29:1542-9.
34. Rizzo L, Tedeschi A, Fallani E, Coppelli A, Vallini V, Iacopi E, et al. Custom-made orthesis and shoes in a structured follow-up program reduces the incidence of neuropathic ulcers in high-risk diabetic foot patients. Int J Low Extrem Wounds 2012;11:59-64.
35. Steed DL, Attinger C, Colaizzi T, Crossland M, Franz M, Harkless L, et al. Guidelines for the treatment of diabetic ulcers. Wound Repair Regen 2006;14:680-92.
36. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:837-53.
37. Hasan R, Firwana B, Elraiyah T, Domecq JP, Prutsky G, Nabhan M, et al. A systematic review and meta-analysis of glycemic control for the prevention of diabetic foot syndrome. J Vasc Surg 2016;63(Suppl):22S-8S.
38. Christman AL, Selvin E, Margolis DJ, Lazarus GS, Garza LA. Hemoglobin A1c predicts healing rate in diabetic wounds. J Invest Dermatol 2011;131:2121-7.
39. Adam DJ, Beard JD, Cleveland T, Bell J, Bradbury AW, Forbes JF, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. Lancet 2005;366:1925-34.
40. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45(Suppl S):S5-67.
41. Bus SA. Priorities in offloading the diabetic foot. Diabetes Metab Res Rev 2012;28(Suppl 1):54-9.
42. Cavanagh PR, Bus SA. Off-loading the diabetic foot for ulcer prevention and healing. J Vasc Surg 2010;52(Suppl):37S-43S.
43. Lewis J, Lipp A. Pressure-relieving interventions for treating diabetic foot ulcers. Cochrane Database Syst Rev 2013;1:CD002302.
44. Snyder RJ, Kirsner RS, Warriner RA 3rd, Lavery LA, Hanft JR, Sheehan P. Consensus recommendations on advancing the standard of care for treating neuropathic foot ulcers in patients with diabetes. Ostomy Wound Manage 2010;56(Suppl):S1-24.
45. Lavery LA, Armstrong DG, Wunderlich RP, Tredwell JL, Boulton AJ. Predictive value of foot pressure assessment as part of a population-based diabetes disease management program. Diabetes Care 2003;26:1069-73.
46. Boulton AJ, Kirsner RS, Vileikyte L. Clinical practice. Neuropathic diabetic foot ulcers. N Engl J Med 2004;351:48-55.
47. Frykberg RG. Diabetic foot ulcerations: management and adjunctive therapy. Clin Podiatr Med Surg 2003;20:709-28.
48. Game FL, Hinchliffe RJ, Apelqvist J, Armstrong DG, Bakker K, Hartemann A, et al. A systematic review of interventions to enhance the healing of chronic ulcers of the foot in diabetes. Diabetes Metab Res Rev 2012;28(Suppl 1):119-41.
49. Arts ML, Waaijman R, de Haart M, Keukenkamp R, Nollet F, Bus SA. Offloading effect of therapeutic footwear in patients with diabetic neuropathy at high risk for plantar foot ulceration. Diabet Med 2012;29:1534-41.
50. Bus SA, Valk GD, van Deursen RW, Armstrong DG, Caravaggi C, Hlavacek P, et al. Specific guidelines on footwear and offloading. Diabetes Metab Res Rev 2008;24(Suppl 1):S192-3.
51. Bus SA, Valk GD, van Deursen RW, Armstrong DG, Caravaggi C, Hlavacek P, et al. The effectiveness of footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in diabetes: a systematic review. Diabetes Metab Res Rev 2008;24(Suppl 1):S162-80.
52. Paton J, Bruce G, Jones R, Stenhouse E. Effectiveness of insoles used for the prevention of ulceration in the neuropathic diabetic foot: a systematic review. J Diabetes Complications 2011;25:52-62.
53. Apelqvist J, Bakker K, van Houtum WH, Schaper NC. The development of global consensus guidelines on the management of the diabetic foot. Diabetes Metab Res Rev 2008;24(Suppl 1):S116-8.
54. Bakker K, Schaper NC. The development of global consensus guidelines on the management and prevention of the diabetic foot 2011. Diabetes Metab Res Rev 2012;28(Suppl 1):116-8.
55. Wu SC, Jensen JL, Weber AK, Robinson DE, Armstrong DG. Use of pressure offloading devices in diabetic foot ulcers: do we practice what we preach? Diabetes Care 2008;31:2118-9.
56. Waaijman R, Keukenkamp R, de Haart M, Polomski WP, Nollet F, Bus SA. Adherence to wearing prescription custom-made footwear in patients with diabetes at high risk for plantar foot ulceration. Diabetes Care 2013;36:1613-8.
57. Armstrong DG, Lavery LA, Wu S, Boulton AJ. Evaluation of removable and irremovable cast walkers in the healing of diabetic foot wounds: a randomized controlled trial. Diabetes Care 2005;28:551-4.
58. Armstrong DG, Nguyen HC, Lavery LA, van Schie CH, Boulton AJ, Harkless LB. Off-loading the diabetic foot wound: a randomized clinical trial. Diabetes Care 2001;24:1019-22.
59. Armstrong DG, Short B, Nixon BP, Boulton AJ. Technique for fabrication of an "instant" total contact cast for treatment of neuropathic diabetic foot ulcers. J Am Podiatr Med Assoc 2002;92:405-8.
60. Birke JA, Pavich MA, Patout CA Jr, Horswell R. Comparison of forefoot ulcer healing using alternative off-loading methods in patients with diabetes mellitus. Adv Skin Wound Care 2002;15:210-5.
61. Burden AC, Jones GR, Jones R, Blandford RL. Use of the "Scotchcast boot" in treating diabetic foot ulcers. Br Med J (Clin Res Ed) 1983;286:1555-7.

62. Faglia E, Caravaggi C, Clerici G, Sganzaroli A, Curci V, Vailati W, et al. Effectiveness of removable walker cast versus nonremovable fiberglass off-bearing cast in the healing of diabetic plantar foot ulcer: a randomized controlled trial. Diabetes Care 2010;33:1419-23.
63. Mueller MJ, Diamond JE, Sinacore DR, Delitto A, Blair VP 3rd, Drury DA, et al. Total contact casting in treatment of diabetic plantar ulcers. Controlled clinical trial. Diabetes Care 1989;12:384-8.
64. Katz IA, Harlan A, Miranda-Palma B, Prieto-Sanchez L, Armstrong DG, Bowker JH, et al. A randomized trial of two irremovable offloading devices in the management of neuropathic diabetic foot ulcers. Diabetes Care 2005;28:555-9.
65. Knowles EA, Armstrong DG, Hayat SA, Khawaja KI, Malik RA, Boulton AJ. Offloading diabetic foot wounds using the Scotchcast boot: a retrospective study. Ostomy Wound Manage 2002;48:50-3.
66. Wukich DK, Motko J. Safety of total contact casting in high-risk patients with neuropathic foot ulcers. Foot Ankle Int 2004;25:556-60.
67. Nube VL, Molyneaux L, Yue DK. Biomechanical risk factors associated with neuropathic ulceration of the hallux in people with diabetes mellitus. J Am Podiatr Med Assoc 2006;96:189-97.
68. Piaggesi A, Macchiarini S, Rizzo L, Palumbo F, Tedeschi A, Nobili LA, et al. An off-the-shelf instant contact casting device for the management of diabetic foot ulcers: a randomized prospective trial versus traditional fiberglass cast. Diabetes Care 2007;30:586-90.
69. Hissink RJ, Manning HA, van Baal JG. The MABAL shoe: an alternative method in contact casting for the treatment of neuropathic diabetic foot ulcers. Foot Ankle Int 2000;21:320-3.
70. Shaw JE, Hsi WL, Ulbrecht JS, Norkitis A, Becker MB, Cavanagh PR. The mechanism of plantar unloading in total contact casts: implications for design and clinical use. Foot Ankle Int 1997;18:809-17.
71. Caravaggi C, Sganzaroli A, Fabbi M, Cavaiani P, Pogliaghi I, Ferraresi R, et al. Nonwindowed nonremovable fiberglass off-loading cast versus removable pneumatic cast (AircastXP Diabetic Walker) in the treatment of neuropathic noninfected plantar ulcers: a randomized prospective trial. Diabetes Care 2007;30:2577-8.
72. Ha Van G, Siney H, Hartmann-Heurtier A, Jacqueminet S, Greau F, Grimaldi A. Nonremovable, windowed, fiberglass cast boot in the treatment of diabetic plantar ulcers: efficacy, safety, and compliance. Diabetes Care 2003;26:2848-52.
73. Nabuurs-Franssen MH, Sleegers R, Huijberts MS, Wijnen W, Sanders AP, Walenkamp G, et al. Total contact casting of the diabetic foot in daily practice: a prospective follow-up study. Diabetes Care 2005;28:243-7.
74. Frigg A, Pagenstert G, Schafer D, Valderrabano V, Hintermann B. Recurrence and prevention of diabetic foot ulcers after total contact casting. Foot Ankle Int 2007;28:64-9.
75. Chantelau E. Half-shoes for off-loading diabetic plantar ulcers. Diabetes Care 2001;24:2016.
76. Armstrong DG, Lavery LA, Kimbriel HR, Nixon BP, Boulton AJ. Activity patterns of patients with diabetic foot ulceration: patients with active ulceration may not adhere to a standard pressure off-loading regimen. Diabetes Care 2003;26:2595-7.
77. Boulton AJ, Armstrong DG. Trials in neuropathic diabetic foot ulceration: time for a paradigm shift? Diabetes Care 2003;26:2689-90.
78. Bakker K, Apelqvist J, Schaper NC. Practical guidelines on the management and prevention of the diabetic foot 2011. Diabetes Metab Res Rev 2012;28(Suppl 1):225-31.
79. Edmonds ME, Blundell MP, Morns ME, Thomas EM, Cotton LT, Watkins PJ. Improved survival of the diabetic foot: the role of a specialized foot clinic. Q J Med 1986;60:763-71.
80. Frykberg RG, Lavery LA, Pham H, Harvey C, Harkless L, Veves A. Role of neuropathy and high foot pressures in diabetic foot ulceration. Diabetes Care 1998;21:1714-9.
81. Armstrong DG, Lavery LA. Plantar pressures are higher in diabetic patients following partial foot amputation. Ostomy Wound Manage 1998;44:30-2. 34, 36 passim.
82. Veves A, Murray HJ, Young MJ, Boulton AJ. The risk of foot ulceration in diabetic patients with high foot pressure: a prospective study. Diabetologia 1992;35:660-3.
83. Frykberg RG, Bevilacqua NJ, Habershaw G. Surgical off-loading of the diabetic foot. J Vasc Surg 2010;52(Suppl):44S-58S.
84. Elraiyah T, Prutsky G, Domecq JP, Tsapas A, Nabhan M, Frykberg RG, et al. A systematic review and meta-analysis of off-loading methods for diabetic foot ulcers. J Vasc Surg 2016;63(Suppl):59S-68S.
85. Palestro CJ, Love C. Nuclear medicine and diabetic foot infections. Semin Nucl Med 2009;39:52-65.
86. Pecoraro RE, Ahroni JH, Boyko EJ, Stensel VL. Chronology and determinants of tissue repair in diabetic lower-extremity ulcers. Diabetes 1991;40:1305-13.
87. Lavery LA, Armstrong DG, Peters EJ, Lipsky BA. Probe-to-bone test for diagnosing diabetic foot osteomyelitis: reliable or relic? Diabetes Care 2007;30:270-4.
88. Lipsky BA. Osteomyelitis of the foot in diabetic patients. Clin Infect Dis 1997;25:1318-26.
89. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, et al. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2004;39:885-910.
90. Dinh T, Snyder G, Veves A. Current techniques to detect foot infection in the diabetic patient. Int J Low Extrem Wounds 2010;9:24-30.
91. Grayson ML, Gibbons GW, Balogh K, Levin E, Karchmer AW. Probing to bone in infected pedal ulcers. A clinical sign of underlying osteomyelitis in diabetic patients. JAMA 1995;273:721-3.
92. Aragon-Sanchez J, Lipsky BA, Lazaro-Martinez JL. Diagnosing diabetic foot osteomyelitis: is the combination of probe-to-bone test and plain radiography sufficient for high-risk inpatients? Diabet Med 2011;28:191-4.
93. Butalia S, Palda VA, Sargeant RJ, Detsky AS, Mourad O. Does this patient with diabetes have osteomyelitis of the lower extremity? JAMA 2008;299:806-13.
94. Lipsky BA, Peters EJ, Senneville E, Berendt AR, Embil JM, Lavery LA, et al. Expert opinion on the management of infections in the diabetic foot. Diabetes Metab Res Rev 2012;28(Suppl 1):163-78.
95. International best practice guidelines: wound management in diabetic foot ulcers. Wounds International. Available at: www.woundsinternational.com. Accessed November 13, 2015.
96. Snyder RJ, Cardinal M, Dauphinee DM, Stavosky J. A post-hoc analysis of reduction in diabetic foot ulcer size at 4 weeks as a predictor of healing by 12 weeks. Ostomy Wound Manage 2010;56:44-50.
97. Cardinal M, Eisenbud DE, Phillips T, Harding K. Early healing rates and wound area measurements are reliable predictors of later complete wound closure. Wound Repair Regen 2008;16:19-22.
98. Lavery LA, Barnes SA, Keith MS, Seaman JW Jr, Armstrong DG. Prediction of healing for postoperative diabetic foot wounds based on early wound area progression. Diabetes Care 2008;31:26-9.
99. Sheehan P, Jones P, Caselli A, Giurini JM, Veves A. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. Diabetes Care 2003;26:1879-82.
100. Lepäntalo M, Apelqvist J, Setacci C, Ricco JB, de Donato G, Becker F, et al. Chapter V: diabetic foot. Eur J Vasc Endovasc Surg 2011;42(Suppl 2):S60-74.
101. Greer N, Foman N, Dorrian J, Fitzgerald P, MacDonald R, Rutks I, et al. Advanced wound care therapies for non-healing diabetic, venous, and arterial ulcers: a systematic review. Ann Intern Med 2013;159:532-42.
102. Dumville JC, Soares MO, O'Meara S, Cullum N. Systematic review and mixed treatment comparison: dressings to heal diabetic foot ulcers. Diabetologia 2012;55:1902-10.
103. Jeffcoate WJ, Price PE, Phillips CJ, Game FL, Mudge E, Davies S, et al. Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes. Health Technol Assess 2009;13:1-86. iii-iv.
104. Dumville JC, O'Meara S, Deshpande S, Speak K. Hydrogel dressings for healing diabetic foot ulcers. Cochrane Database Syst Rev 2013;7:CD009101.
105. Dumville JC, Deshpande S, O'Meara S, Speak K. Hydrocolloid dressings for healing diabetic foot ulcers. Cochrane Database Syst Rev 2013;8:CD009099.

106. Dumville JC, Deshpande S, O'Meara S, Speak K. Foam dressings for healing diabetic foot ulcers. Cochrane Database Syst Rev 2013;6:CD009111.
107. Dumville JC, O'Meara S, Deshpande S, Speak K. Alginate dressings for healing diabetic foot ulcers. Cochrane Database Syst Rev 2013;6:CD009110.
108. Jull AB, Walker N, Deshpande S. Honey as a topical treatment for wounds. Cochrane Database Syst Rev 2013;2:CD005083.
109. Siavash M, Shokri S, Haghighi S, Shahtalebi MA, Farajzadehgan Z. The efficacy of topical royal jelly on healing of diabetic foot ulcers: a double-blind placebo-controlled clinical trial. Int Wound J 2015;12:137-42.
110. Moghazy AM, Shams ME, Adly OA, Abbas AH, El-Badawy MA, Elsakka DM, et al. The clinical and cost effectiveness of bee honey dressing in the treatment of diabetic foot ulcers. Diabetes Res Clin Pract 2010;89:276-81.
111. Trial C, Darbas H, Lavigne JP, Sotto A, Simoneau G, Tillet Y, et al. Assessment of the antimicrobial effectiveness of a new silver alginate wound dressing: a RCT. J Wound Care 2010;19:20-6.
112. Storm-Versloot MN, Vos CG, Ubbink DT, Vermeulen H. Topical silver for preventing wound infection. Cochrane Database Syst Rev 2010;3:CD006478.
113. Jude EB, Apelqvist J, Spraul M, Martini J. Prospective randomized controlled study of Hydrofiber dressing containing ionic silver or calcium alginate dressings in non-ischaemic diabetic foot ulcers. Diabet Med 2007;24:280-8.
114. Bergin SM, Wraight P. Silver based wound dressings and topical agents for treating diabetic foot ulcers. Cochrane Database Syst Rev 2006;1:CD005082.
115. Voigt J, Driver VR. Hyaluronic acid derivatives and their healing effect on burns, epithelial surgical wounds, and chronic wounds: a systematic review and meta-analysis of randomized controlled trials. Wound Repair Regen 2012;20:317-31.
116. Gottrup F, Apelqvist J. Present and new techniques and devices in the treatment of DFU: a critical review of evidence. Diabetes Metab Res Rev 2012;28(Suppl 1):64-71.
117. Edwards J, Stapley S. Debridement of diabetic foot ulcers. Cochrane Database Syst Rev 2010;1:CD003556.
118. Abouaesha F, van Schie CHM, Griffths GD, Young RJ, Boulton AJM. Plantar tissue thickness is related to peak plantar pressure in the high-risk diabetic foot. Diabetes Care 2001;24:1270-4.
119. Cornell RS, Meyr AJ, Steinberg JS, Attinger CE. Debridement of the noninfected wound. J Vasc Surg 2010;52(Suppl):31S-6S.
120. Elraiyah T, Domecq JP, Prutsky G, Tsapas A, Nabhan M, Frykberg RG, et al. A systematic review and meta-analysis of débridement methods for chronic diabetic foot ulcers. J Vasc Surg 2016;63(Suppl):37S-45S.
121. Elraiyah T, Tsapas A, Prutsky G, Domecq JP, Hasan R, Firwana B, et al. A systematic review and meta-analysis of adjunctive therapies in diabetic foot ulcers. J Vasc Surg 2016;63(Suppl):46S-58S.
122. Blume PA, Walters J, Payne W, Ayala J, Lantis J. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. Diabetes Care 2008;31:631-6.
123. Farah R, Gantus M, Kogan L. [Vacuum-assisted therapy for various wound types including diabetic foot ulcer]. Harefuah 2011;150:222-6. 306, 305.
124. Karatepe O, Eken I, Acet E, Unal O, Mert M, Koc B, et al. Vacuum assisted closure improves the quality of life in patients with diabetic foot. Acta Chir Belg 2011;111:298-302.
125. Nain PS, Uppal SK, Garg R, Bajaj K, Garg S. Role of negative pressure wound therapy in healing of diabetic foot ulcers. J Surg Tech Case Rep 2011;3:17-22.
126. Ulusal AE, Sahin MS, Ulusal B, Cakmak G, Tuncay C. Negative pressure wound therapy in patients with diabetic foot. Acta Orthop Traumatol Turc 2011;45:254-60.
127. Nather A, Chionh SB, Han AY, Chan PP, Nambiar A. Effectiveness of vacuum-assisted closure (VAC) therapy in the healing of chronic diabetic foot ulcers. Ann Acad Med Singapore 2010;39:353-8.
128. Akbari A, Moodi H, Ghiasi F, Sagheb HM, Rashidi H. Effects of vacuum-compression therapy on healing of diabetic foot ulcers: randomized controlled trial. J Rehabil Res Dev 2007;44:631-6.
129. Vig S, Dowsett C, Berg L, Caravaggi C, Rome P, Birke-Sorensen H, et al. Evidence-based recommendations for the use of negative pressure wound therapy in chronic wounds: steps towards an international consensus. J Tissue Viability 2011;20(Suppl 1):S1-18.
130. Xie X, McGregor M, Dendukuri N. The clinical effectiveness of negative pressure wound therapy: a systematic review. J Wound Care 2010;19:490-5.
131. Vikatmaa P, Juutilainen V, Kuukasjarvi P, Malmivaara A. Negative pressure wound therapy: a systematic review on effectiveness and safety. Eur J Vasc Endovasc Surg 2008;36:438-48.
132. Frykberg RG, Williams DV. Negative-pressure wound therapy and diabetic foot amputations: a retrospective study of payer claims data. J Am Podiatr Med Assoc 2007;97:351-9.
133. Lavery LA, Boulton AJ, Niezgoda JA, Sheehan P. A comparison of diabetic foot ulcer outcomes using negative pressure wound therapy versus historical standard of care. Int Wound J 2007;4:103-13.
134. Steed DL. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity diabetic ulcers. Diabetic Ulcer Study Group. J Vasc Surg 1995;21:71-8; discussion: 79-81.
135. Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebo-controlled double-blind study. Diabetes Care 1998;21:822-7.
136. d'Hemecourt P, Smiell J, Karim M. Sodium carboxymethylcellulose aqueous-based gel vs. becaplermin gel in patients with nonhealing lower-extremity diabetic ulcers. Wounds 1998;10:69-75.
137. Smiell JM, Wieman TJ, Steed DL, Perry BH, Sampson AR, Schwab BH. Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. Wound Repair Regen 1999;7:335-46.
138. Kantor J, Margolis DJ. Treatment options for diabetic neuropathic foot ulcers: a cost-effectiveness analysis. Dermatol Surg 2001;27:347-51.
139. U.S. Food and Drug Administration. Regranex (becaplermin) gel 0.01% October 2008. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm121631.htm. Accessed November 13, 2015.
140. Curran MP, Plosker GL. Bilayered bioengineered skin substitute (Apligraf): a review of its use in the treatment of venous leg ulcers and diabetic foot ulcers. BioDrugs 2002;16:439-55.
141. Veves A, Falanga V, Armstrong DG, Sabolinski ML. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. Diabetes Care 2001;24:290-5.
142. Redekop WK, McDonnell J, Verboom P, Lovas K, Kalo Z. The cost effectiveness of Apligraf treatment of diabetic foot ulcers. Pharmacoeconomics 2003;21:1171-83.
143. Marston WA. Dermagraft, a bioengineered human dermal equivalent for the treatment of chronic nonhealing diabetic foot ulcer. Expert Rev Med Devices 2004;1:21-31.
144. Marston WA, Hanft J, Norwood P, Pollak R. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. Diabetes Care 2003;26:1701-5.
145. Hanft JR, Surprenant MS. Healing of chronic foot ulcers in diabetic patients treated with a human fibroblast-derived dermis. J Foot Ankle Surg 2002;41:291-9.
146. Niezgoda JA, Van Gils CC, Frykberg RG, Hodde JP. Randomized clinical trial comparing OASIS Wound Matrix to Regranex Gel for diabetic ulcers. Adv Skin Wound Care 2005;18(Pt 1):258-66.
147. Reyzelman A, Crews RT, Moore JC, Moore L, Mukker JS, Offutt S, et al. Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic

foot ulcers: a prospective, randomised, multicentre study. Int Wound J 2009;6:196-208.
148. Fife CE, Smart DR, Sheffield PJ, Hopf HW, Hawkins G, Clarke D. Transcutaneous oximetry in clinical practice: consensus statements from an expert panel based on evidence. Undersea Hyperb Med 2009;36:43-53.
149. Cavanagh PR, Lipsky BA, Bradbury AW, Botek G. Treatment for diabetic foot ulcers. Lancet 2005;366:1725-35.
150. Armstrong DG, Kanda VA, Lavery LA, Marston W, Mills JL, Boulton AJM. Mind the gap: the disparity between research funding and costs of care for diabetic foot ulcers. Diabetes Care 2013;36:1815-7.
151. Hinchliffe RJ, Andros G, Apelqvist J, Bakker K, Friederichs S, Lammer J, et al. A systematic review of the effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral arterial disease. Diabetes Metab Res Rev 2012;28(Suppl 1):179-217.
152. Apelqvist J, Elgzyri T, Larsson J, Londahl M, Nyberg P, Thorne J. Factors related to outcome of neuroischemic/ischemic foot ulcer in diabetic patients. J Vasc Surg 2011;53:1582-8.e2.
153. Schaper NC, Andros G, Apelqvist J, Bakker K, Lammer J, Lepantalo M, et al. Diagnosis and treatment of peripheral arterial disease in diabetic patients with a foot ulcer. A progress report of the International Working Group on the Diabetic Foot. Diabetes Metab Res Rev 2012;28(Suppl 1):218-24.
154. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care 1998;21:855-9.
155. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: a survival prediction model to facilitate clinical decision making. J Vasc Surg 2010;51(Suppl):52S-68S.
156. Morbach S, Furchert H, Groblinghoff U, Hoffmeier H, Kersten K, Klauke GT, et al. Long-term prognosis of diabetic foot patients and their limbs: amputation and death over the course of a decade. Diabetes Care 2012;35:2021-7.
157. Yost ML. Diabetic foot ulcers, peripheral arterial disease and critical limb ischemia. Atlanta, Ga: The Sage Group; 2011.
158. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001;286:1317-24.
159. Morbach S, Lutale JK, Viswanathan V, Mollenberg J, Ochs HR, Rajashekar S, et al. Regional differences in risk factors and clinical presentation of diabetic foot lesions. Diabet Med 2004;21:91-5.
160. Boulton AJ, Armstrong DG, Albert SF, Frykberg RG, Hellman R, Kirkman MS, et al. Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. Diabetes Care 2008;31:1679-85.
161. Kalani M, Brismar K, Fagrell B, Ostergren J, Jorneskog G. Transcutaneous oxygen tension and toe blood pressure as predictors for outcome of diabetic foot ulcers. Diabetes Care 1999;22:147-51.
162. Faglia E, Clerici G, Caminiti M, Quarantiello A, Curci V, Morabito A. Predictive values of transcutaneous oxygen tension for above-the-ankle amputation in diabetic patients with critical limb ischemia. Eur J Vasc Endovasc Surg 2007;33:731-6.
163. Wang Z, Hasan R, Firwana B, Elraiyah T, Tsapas A, Prokop L, et al. A systematic review and meta-analysis of tests to predict wound healing in diabetic foot. J Vasc Surg 2016;63(Suppl):29S-36S.
164. Faglia E, Dalla Paola L, Clerici G, Clerissi J, Graziani L, Fusaro M, et al. Peripheral angioplasty as the first-choice revascularization procedure in diabetic patients with critical limb ischemia: prospective study of 993 consecutive patients hospitalized and followed between 1999 and 2003. Eur J Vasc Endovasc Surg 2005;29:620-7.
165. Cull DL, Langan EM, Gray BH, Johnson B, Taylor SM. Open versus endovascular intervention for critical limb ischemia: a population-based study. J Am Coll Surg 2010;210:555-61. 561-3.
166. Li Y, Burrows NR, Gregg EW, Albright A, Geiss LS. Declining rates of hospitalization for nontraumatic lower-extremity amputation in the diabetic population aged 40 years or older: U.S., 1988-2008. Diabetes Care 2012;35:273-7.
167. Goodney PP, Holman K, Henke PK, Travis LL, Dimick JB, Stukel TA, et al. Regional intensity of vascular care and lower extremity amputation rates. J Vasc Surg 2013;57:1471-9. 1480.e1-3; discussion: 1479-80.
168. Mills JL Sr. Open bypass and endoluminal therapy: complementary techniques for revascularization in diabetic patients with critical limb ischaemia. Diabetes Metab Res Rev 2008;24(Suppl 1):S34-9.
169. Ihnat DM, Mills JL Sr. Current assessment of endovascular therapy for infrainguinal arterial occlusive disease in patients with diabetes. J Vasc Surg 2010;52(Suppl):92S-5S.
170. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, et al; BASIL trial Participants. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: an intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. J Vasc Surg 2010;51(Suppl):5S-17S.
171. Mills JL Sr, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIfI). J Vasc Surg 2014;59:220-34.e1-2.
172. Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia 2007;50:18-25.
173. Faglia E, Clerici G, Caminiti M, Quarantiello A, Gino M, Morabito A. The role of early surgical debridement and revascularization in patients with diabetes and deep foot space abscess: retrospective review of 106 patients with diabetes. J Foot Ankle Surg 2006;45:220-6.
174. Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. J Am Podiatr Med Assoc 2013;103:2-7.

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