Circulation

AHA SCIENTIFIC STATEMENT

Current Status and Principles for the Treatment and Prevention of Diabetic Foot Ulcers in the Cardiovascular Patient Population: A Scientific Statement From the American Heart Association

Katherine A. Gallagher, MD, FACS, FAHA, Chair; Joseph L. Mills, FACS, MD, Vice Chair; David G. Armstrong, DPM, MD, PhD; Michael S. Conte, MD, FACS, FAHA; Robert S. Kirsner, MD, PhD; Samantha D. Minc, MD, MPH, FACS; Jorge Plutzky, MD, FAHA; Kevin W. Southerland, MD; Marjana Tomic-Canic, PhD; on behalf of the American Heart Association Council on Peripheral Vascular Disease; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Lifestyle and Cardiometabolic Health

ABSTRACT: Despite the known higher risk of cardiovascular disease in individuals with type 2 diabetes, the pathophysiology and optimal management of diabetic foot ulcers (DFUs), a leading complication associated with diabetes, is complex and continues to evolve. Complications of type 2 diabetes, such as DFUs, are a major cause of morbidity and mortality and the leading cause of major lower extremity amputation in the United States. There has recently been a strong focus on the prevention and early treatment of DFUs, leading to the development of multidisciplinary diabetic wound and amputation prevention clinics across the country. Mounting evidence has shown that, despite these efforts, amputations associated with DFUs continue to increase. Furthermore, due to increasing patient complexity of management secondary to comorbid conditions, such as cardiovascular disease, the management of peripheral artery disease associated with DFUs has become increasingly difficult, and care delivery is often episodic and fragmented. Although structured, process-specific approaches exist at individual institutions for the management of DFUs in the cardiovascular patient population, there is insufficient awareness of these principles in the general medicine communities. Furthermore, there is growing interest in better understanding the mechanistic underpinnings of DFUs to better define personalized medicine to improve outcomes. The goals of this scientific statement are to provide salient background information on the complex pathogenesis and current management of DFUs in cardiovascular patients, to guide therapeutic and preventive strategies and future research directions, and to inform public policy makers on health disparities and other barriers to improving and advancing care in this expanding patient population.

Key Words: AHA Scientific Statements ■ amputation, surgical ■ cardiovascular diseases ■ diabetes, type 2 ■ diabetic foot ■ health care disparities ■ health inequities ■ peripheral arterial disease

The number of cardiovascular patients with diabetes and associated diabetic foot disease has dramatically increased during the past decade. Although both type 1 and type 2 diabetes are strongly associated with cardiovascular disease, type 2 diabetes accounts for 95% of patients with diabetes, and, as such, type 2 diabetes is commonly linked to a large proportion of nonhealing diabetic foot ulcers (DFUs). The prevalence of people with diabetes-related lower extremity complications was a staggering 131 million people, or 1.8% of the global population.[1] This dramatic increase, combined with the inherent complexities related to the management of this population, and other factors related to health care delivery and social inequities, as well, all contribute to the unacceptably high amputation rates in the United States. Moreover, because current treatments and algorithms of care are presently suboptimal and not always followed, we will address research progress in this arena while highlighting health

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disparities and translational work that may improve both access to care and treatment options in these patients. Therefore, understanding the prevention and current best management practices for this complex population is vital to reducing the public health burden of this devastating disease. The focus of this scientific statement is to review the latest evidence supporting the prevention and management of diabetic foot disease in the cardiovascular population and advances made in the outcomes, disparities, and translational research space that can improve outcomes for these patients in the near future.

EPIDEMIOLOGY AND STAGING

Epidemiology

Nonhealing wounds in patients with concomitant cardiovascular disease and diabetes constitute a significant public health burden. DFUs constitute wounds below the malleoli in patients with diabetes and are typically caused by a combination of factors, including nerve damage, immune system dysfunction, and peripheral artery disease (PAD) and are frequently associated with trauma to the foot. This is in accordance with the International Working Group on the diabetic foot[2] where DFUs are defined as occurring in patients with current or previously diagnosed diabetes, usually accompanied by neuropathy or PAD in the lower extremity. The lifetime risk of developing a DFU[2] in patients with diabetes is at least 25% and may exceed 34%.[3] Perhaps equally alarming, DFUs constitute one of the most common factors contributing to hospital admission in patients with diabetes, placing a direct burden on an already overwhelmed health care system.[4] Likewise, the direct costs associated with treating DFUs exceed treatment costs for many common forms of cancer.[5] The personal cost for individuals with DFUs is also significant and can be greater than a year's worth of salary, depending on health system and severity of disease,[6] and may also lead to job loss for individuals who cannot work while nonweight bearing. Over the past decade, the epidemiology of lower extremity amputation has been relatively dynamic, particularly in the United States compared with other areas of the world. Although some studies suggest that the overall prevalence of lower extremity amputation appears to have peaked from 2010 to 2015, trends over the past decade clearly suggest that there has been a dramatic increase in amputations among people with diabetes.[6,7] As mentioned, DFUs are primary drivers of hospitalization in the ever-growing diabetes population; hence, these studies suggest a disturbing trend that has the potential to overwhelm our health care system.

The natural history of DFUs is highly morbid, particularly in the cardiovascular population. For example, the presence of a DFU in a patient with diabetes more than doubles expected mortality compared with patients with diabetes without a DFU.[7,8] More than half of DFUs, unfortunately, will become infected,[9] and once infected, at least ≥20% will require some form of amputation. In addition, mortality rate after diabetes-related amputation is worse than amputations performed for other reasons, where the mortality rate in patients with diabetes exceeds 70% at 5 years and increases to 74% at 2 years for those patients with diabetes who are also on renal replacement therapy, a common comorbidity in the cardiovascular/diabetic population.[9] This mortality rate exceeds all but the most aggressive forms of cancer, yet the management and treatment algorithms for these patients remain less well defined and often unclear to the primary physicians treating these patients on a regular basis.[5]

Staging

Although it is well established that 85% of diabetes-related amputations are preceded by a DFU, with early, high-quality care, a higher percentage of DFUs can heal. The current standard of care includes surgical debridement, pressure offloading, attention to infection, assessment of circulation, and, when needed, revascularization; these interventions are the mainstays of current treatment and will be discussed in detail later in this document. However, the first step in ensuring high-quality care begins with appropriate taxonomy and risk assessment of each patient presenting with a DFU. Several validated classification systems exist to assess wounds,[10] ischemia,[11] and foot infection, and these are reviewed in Supplemental Table 1.[12,13] Many of the previously used classification systems, however, generally focused primarily on one wound or limb factor (eg, wound depth, severity of ischemia, severity of infection) without allowing for description and interaction of the presence or severity of additional contributing factors to exist simultaneously. To combat this issue, the Society for Vascular Surgery Wound, Ischemia and Foot Infection (WIfI) threatened limb classification system[14] brought these critical elements together, has been widely validated, and is summarized in Figure 1. The WIfI system is based on wound severity, extent of infection, and perfusion status, and it provides a reliable model for determining amputation risk while aiding in the clinical decision-making process.[15] It is important that WIfI mandates not only pulse palpation but also objective measurements of foot perfusion (ankle brachial index and toe systolic pressure or transcutaneous oxygen measurement [$TcPo_2$]) to avoid failure to identify ischemia as a potentially correctable, contributory factor for nonhealing DFU. Although not specific to DFUs, the WIfI classification is extremely useful in the risk assessment of patients with DFU because it consists of ordinal severity grading of tissue loss, ischemia, and infection on a 4-point scale and is dedicated to staging overall limb threat, analogous to the tumor, node, metastasis (TNM) classification for cancers. The 64 total WIfI combinations have been grouped into 4 clinical stages that correlate

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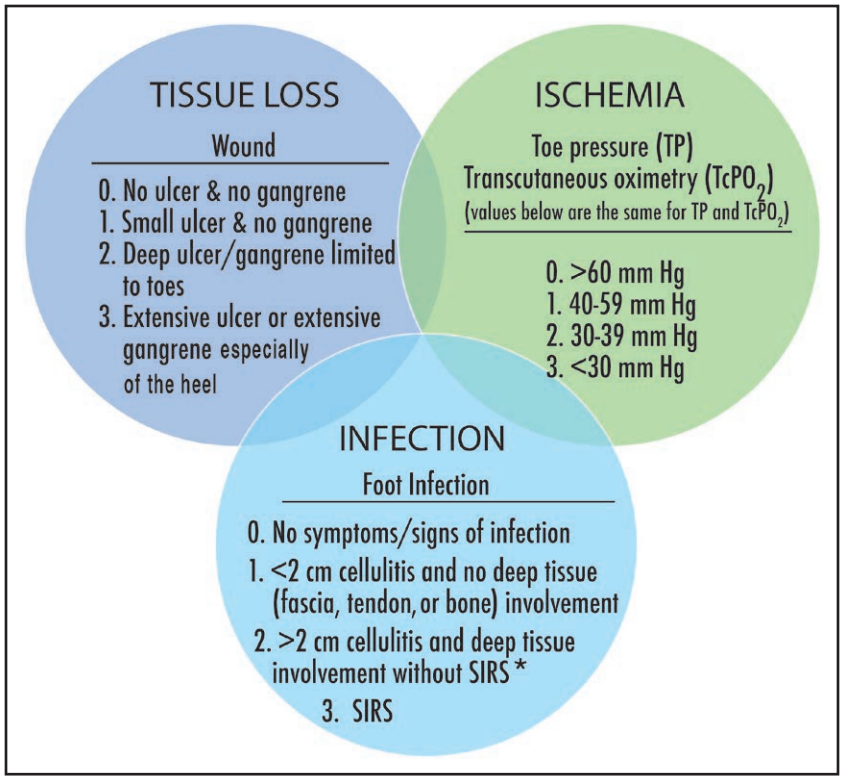

Figure 1. WiFi staging criteria for DFUs.
SIRS indicates Systemic Inflammatory Response Score.

with the expected risk of major amputation at 1 year. WIfI staging allows the clinician to triage urgency, identify the current dominant condition or conditions, and sequence treatment accordingly.[16] For example, patients presenting with WIfI clinical stage 4 limb severity are at extremely high risk of major limb amputation, mandating an expedited treatment approach to preserve functional limb salvage. WIfI staging also allows for the serial assessment of treatment response over time, an important factor for patients with DFUs.[11,17] For these reasons, the WIfI is the preferred classification system for patients presenting with a DFU and should be used widely in the initial assessment of any patient presenting with a DFU.

DISPARITIES IN DFUs

Health Disparities Associated With DFU Related Amputations

Disparities in amputation rates for patients with diabetes have been identified as an area of national concern since 2003.[18] Since that time, multiple studies have identified variation in amputation risk on the basis of socioeconomic, racial, ethnic, and geographic (rural- and urban-dwelling) status,[19–25] and there has been an exponential growth in publications on the subject. Although the risk for amputation is highest in communities with higher levels of traditional risk factors, such as diabetes, cardiovascular disease, and tobacco use, it is also disproportionately higher in disenfranchised populations affected by high economic hardship and chronic external stressors.[20,26] Disparities in amputation rates, thus, serve as a marker for structural inequities in health care access, quality of health care, and nonmedical factors, such as food security, transportation, and housing stability (ie, the Social Determinants of Health). In addition, diabetes-related amputation in some cases may be preventable with access to higher quality medical, podiatric, and vascular care,[27–31] and as such, reducing disparities in amputation rates has been adopted as a leading health indicator and national objective for achieving equity in the treatment of diabetes across the country.[32]

Disparities Related to Ethnicity and Race

There is a significant body of literature describing racial and ethnic disparities in amputation rates for both chronic limb-threatening ischemia (CLTI) and diabetes,[19,30,33–44] and although it is often argued that the increased risk of race and ethnicity cannot be separated from confounders, such as socioeconomic status, numerous studies have identified that, even after controlling for risk factors, such as socioeconomic status, comorbidities, and advanced disease, Black and African American and Hispanic and Latino patients are more likely to undergo major amputation for CLTI and diabetes than White patients.[19,25,33,36,39–41,44] Similar findings have been reported in Native American populations.[45,46] It is even more troubling that there is ample evidence to support that race and ethnicity is also an independent predictor for primary

amputation (ie, amputation without attempt at revascularization),[33,36,38,39,41,44,47,48] suggesting that there are other factors at play that have yet to be identified or measured in a meaningful way. These factors may include structural inequities[49,50] and implicit bias,[51] among other factors.

Geographic Disparities

Rural-dwelling populations have been repeatedly identified as a major at-risk group for health disparities, including DFU-associated amputation. Studies suggest that rural-dwelling patients undergo amputation at rates 51.3% higher than non-rural-dwelling patients,[52] and there are data to support that heavily rural-dwelling areas have higher amputation rates compared with the rest of the country.[23,24,53] One potential explanation for these findings is that rural-dwelling patients tend to be medically underresourced and deal with significant physical and cultural barriers to accessing quality care. In addition, rural-dwelling populations tend to be older, more economically depressed, and have higher levels of chronic disease, such as diabetes, and riskier health behaviors than their urban-dwelling counterparts.[54] It is interesting to note, however, that even when controlling for comorbidities and other risk factors, studies have demonstrated that geographic variation in amputation risk continues to exist,[23] further reinforcing the hypothesis that there are other variables involved that remain unknown.

Intersectionality

Intersectionality is the theory that individuals' multiple identities within social systems compound and exacerbate experiences of ill health.[55,56] The effect of intersectionality in amplifying risk for amputation also finds support in the literature. Examples of the effect of intersectionality in amputation disparities include findings that rural-dwelling patients identifying as Black have a higher risk for primary amputation than their urban-dwelling Black counterparts[48] and a higher risk of amputation for DFUs than would otherwise be expected if the risk of amputation associated with rural-dwelling residence and Black and African American race were simply additive.[57] There is also literature suggesting that Black and African American women are at significantly higher risk for amputation than Black and African American men.[58] Intersectionality highlights the complexity of health disparities and suggests that preventive strategies must engage at risk communities to better understand and effectively address health disparities.

PATHOGENESIS OF DFUs IN CARDIOVASCULAR PATIENTS

The mechanisms underlying nonhealing wounds in patients with diabetes are multifactorial. One general approach to organize thinking about nonhealing DFUs is to consider mechanistic inputs common to atherosclerosis and vascular disease, both in general and in patients with diabetes, and pathogenic drivers more specific to DFUs. Defining the underlying factors responsible for nonhealing wounds in a person with diabetes is particularly relevant on several fronts, because information that can help guide management, whether decreasing initial wound occurrence and promoting wound healing while also highlighting where mechanistic understanding is lacking, can help stimulate further investigation and new therapeutic options (Figure 2).

Cardiovascular Risk Factors Associated With Macrovascular and Microvascular Disease in Patients With DFUs

DFUs are strongly influenced by vascular disease, which helps explain the overlap of this common problem with factors that promote atherosclerosis, whether it be macrovascular or microvascular. Macrovascular atherosclerotic occlusive disease can limit the available perfusion to the distal extremities, whereas microvascular disease can also contribute to the development of diabetic wounds. Although it is hard to separate the factors associated with macro- or microvascular disease, hypercholesterolemia and hypertension are more often associated with macrovascular disease development, where hyperglycemia is most often associated with microvascular disease. Many cardiovascular risk factors, such as tobacco use, are strongly associated with worsening of both macro- and microvascular disease, and it is important to note that both processes contribute to nonhealing in DFUs. The role of hypercholesterolemia in macrovascular atherosclerosis, and the benefits of low-density lipoprotein cholesterol lowering in the reduction of atherosclerotic complications in patients with diabetes, as well, is unequivocal; however, as is often the case in diabetic wound healing, direct evidence specifically linking some well-established cardiovascular risk factors, including hypercholesterolemia and hypertension, to diabetic wound healing has not been demonstrated. Distinct from hypercholesterolemia, dyslipidemia in the form of hypertriglyceridemia and low high-density lipoprotein levels may be especially relevant to nonhealing wounds in DFUs. Triglyceride handling, through metabolism of triglyceride-rich lipoproteins, such as the interaction of very low-density lipoproteins with lipoprotein lipase, occurs primarily in small arterioles, raising the potential for a more direct role in wound healing. High-density lipoproteins may be especially involved in mitigating oxidative stress and other aspects of redox balance and may also be relevant for small vessel disease and wound healing in diabetes. The overlap between macrovascular and microvascular disease is clearly extensive, but therapies targeting microvasculature disease are limited at present.

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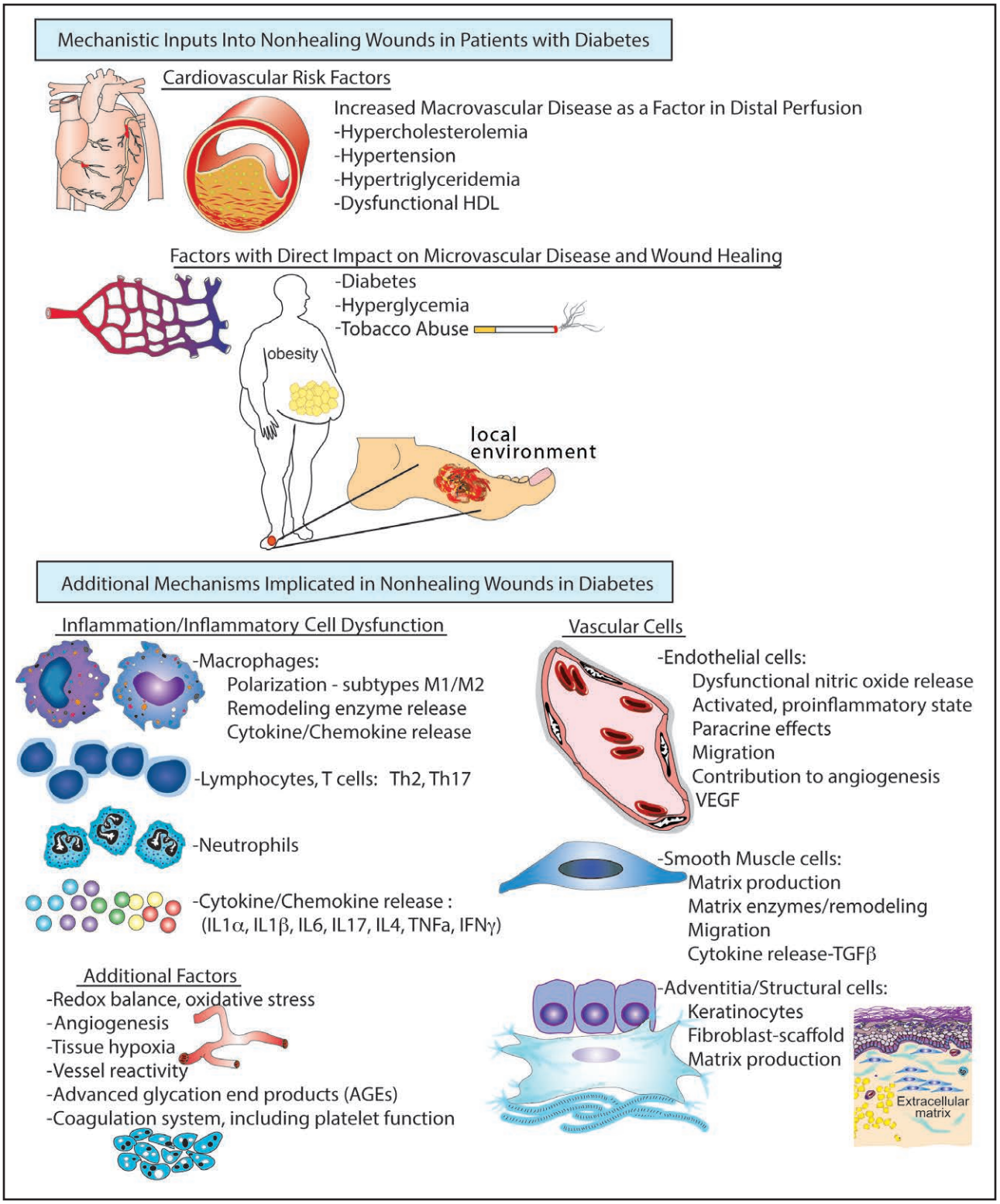

Figure 2. Mechanisms for nonhealing wounds in diabetes.
HDL indicates high-density lipoprotein; IL, interleukin; INFγ, interferon γ; TGF, transforming growth factor; Th2, T helper 2 cell; Th16, T helper 16 cell; TNFα, tumor necrosis factor α; and VEGF, vascular endothelial growth factor.

Another risk factor strongly associated with diabetic macrovascular and microvascular disease, and wound healing, as well, is hyperglycemia. Although often linked, both diabetes and hyperglycemia are considered independent major risk factors contributing to small vessel disease by altering properties of skin and underlying

tissue that predispose to injury, while also limiting the capacity to heal. Diabetes and hyperglycemia can contribute to secondary components that promote nonhealing wounds through their association with factors like endothelial activation, dysregulated inflammation as involves endothelial activation and increased inflammatory cell phenotypes, impaired vessel reactivity, increased oxidative stress, and tissue hypoxia.

Although managing general risk factors that improve vascular disease in patients with diabetes might also affect wound healing, a particularly intriguing issue is whether novel glucose-lowering agents that have shown benefit in reducing cardiovascular events in patients with diabetes, such as glucagon-like peptide 1 receptor agonists and sodium-glucose cotransporter 2 inhibitors, might also affect wound healing, possibly independent of improving distal extremity perfusion. The specific effects of these drugs are still under investigation, and it should be noted that one of the sodium-glucose cotransporter 2 inhibitors, canagliflozin, was examined as part of the CANVAS trial (Canagliflozin Cardiovascular Assessment Study) and was found to be associated with an increased risk of amputation. This initially resulted in a black box warning by the Food and Drug Administration, which has since been removed; however, this drug should be used with extreme caution, or perhaps not at all, in this patient population because the increased risk of limb events likely persists.[59]

Of note, the relationship between hyperglycemia and adverse cardiovascular events is a continuous gradient, as increasingly explored in considering the cardiovascular risk associated with prediabetes. In this regard, making a distinction between hyperglycemia and diabetes may be relevant, as encountered in patients who may have significant hyperglycemia even if the relatively arbitrary thresholds used to define diabetes have not been crossed. The specific effects of these drugs on both macro- and microvascular disease, and DFU healing, as well, requires further investigation.

Sensory Neuropathy Associated With DFUs

Autonomic and sensory neuropathy increases the risk for initial injury to distal extremities due to a loss of proprioception. The initial injury in patients with diabetes may also involve alterations in the skin itself that foster greater disruption in the integument, loss of its protective nature, and other factors, as well. Although peripheral neuropathy is a major risk factor for development of a DFU, this mechanism is well-discussed in other statements from the American Diabetes Association and is beyond the scope of this document.

Cellular Dysfunction Associated With DFUs

Wound healing depends on a tightly regulated process that involves many different cells and mediators ranging from platelets and coagulation factors to immune and structural cells.

In addition to factors associated with specific cell functions involved in wound contraction, immune cell dysfunction, associated with diabetes, hinders resistance to infection, further promoting chronic inflammation and polymicrobial infections. Multiple genomic studies using DFU tissue and next-generation sequencing including single-cell RNA sequencing recently underscored deregulated inflammatory response[60] in both keratinocytes and immune cells, suggesting that reactivation of acute wound response would be clinically beneficial. Although many of the factors outlined in the preceding sections alter the existing microvasculature, once injured, the response to this injury is also thought to involve angiogenesis, which has been shown to be impaired in diabetic tissues. The cellular- and tissue-specific factors associated with nonhealing DFUs are shown in Figure 3. Many of these dysfunctional cells and processes are the subject of investigation in an effort to improve cell function and ultimately improve DFU healing.

DIAGNOSTIC CONSIDERATIONS

Early identification and staging (as discussed earlier) of patients with a DFU for contributory factors and amputation risk must be expeditious, especially in patients with diabetes, who often cannot feel their wounds due to the loss of sensation and who also are especially prone to infection due to the cellular dysfunction discussed in the previous section. To standardize diagnosis and treatment, the Global Vascular Guidelines and others recommend prompt WIfI-graded assessment (see Figure 1). To provide accurate staging beyond what can be obtained from the physical examination, several diagnostic tests are needed.

Role of Imaging

Imaging is important to inform a timely diagnosis and ultimately informs management related to infection and impaired perfusion. This is a particularly important component of patients presenting to the emergency department with a DFU who are often experiencing signs of systemic toxicity, which may or may not be related to the DFU.

Imaging to Evaluate Degree of Infection

Plain radiographs are the first-line modality for any patient with diabetes and a foot ulcer >2 weeks in duration or a patient with diabetes suspected of having a nonsuperficial soft tissue infection per Infectious Diseases of Society of America guidelines.[61–63] Plain radiography can also be used to evaluate for articular deformities, including Charcot osteoarthropathy, which is common in patients with diabetes.[64] Findings of gas are an indication

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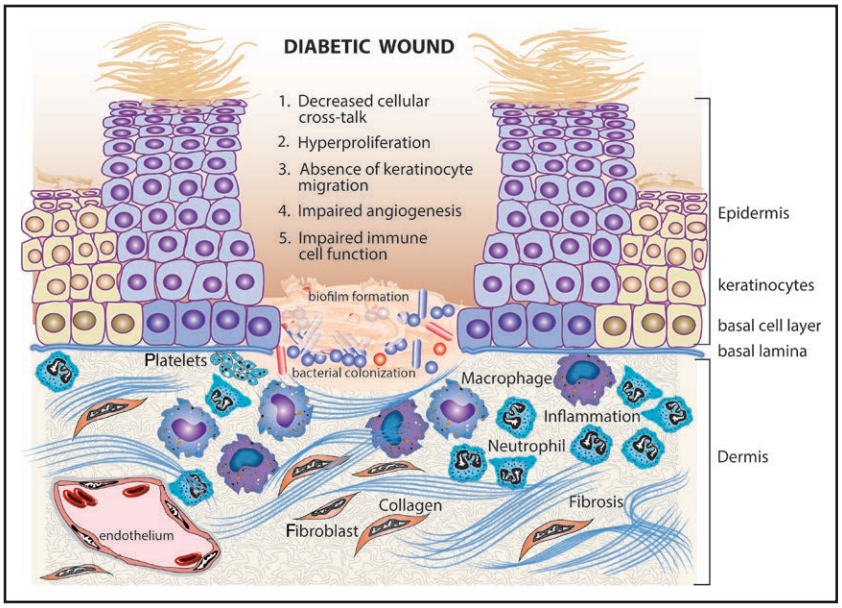

Figure 3. Cellular dysfunction in nonhealing diabetic wounds.

for acute drainage and debridement as discussed below. Although radiography is often used initially, an early diagnosis of osteomyelitis may be difficult to make because the changes on radiographs are often subtle, or absent, in the early stages of the disease process.[65] Osteomyelitis is more often associated with chronic DFUs, and the inability to clear this deep bone infection can complicate DFU healing. If osteomyelitis is strongly suspected despite a negative or equivocal radiograph, or if additional imaging is needed to evaluate the extent of osteomyelitis, an MRI is often indicated. If the patient cannot undergo an MRI for various reasons, a triple-phase bone scan in combination with a tagged white blood cell scan is an acceptable alternative to evaluate for osteomyelitis.[63,66] MRI is useful to identify soft tissue infection when there is concern for soft tissue abscess,[62] and the addition of intravenous gadolinium with the MRI improves the sensitivity for visualizing soft tissue abscess.[67] Newer guidelines suggest a potential role for single-photon emission computed tomography scan with a computed tomography scan and positron emission tomography scan with a computed tomography scan, although single-photon emission computed tomography is often included in bone and white blood cell scans[61,68,69] and can be useful to delineate anatomy and pathological findings that are often helpful with surgical planning.

Imaging to Evaluate Blood Flow and Revascularization Options

As discussed above, patients with diabetes have a high likelihood of concomitant PAD. Thus, in any cardiovascular patient with a DFU, assessment of peripheral perfusion is mandatory because it guides further management strategies.[70] In general, an ankle brachial index alone does not provide reliable results in diabetic patients with noncompressible vessels due to medial calcinosis, and thus a toe systolic pressure or $TcPo_2$ and toe brachial index is needed to determine perfusion to the foot. It is notable that up to 10% of patients with noncompressible ankle brachial indexes will also have noncompressible toe brachial indices.[71] After an initial perfusion defect is identified through the noninvasive testing, additional imaging is needed to identify appropriate revascularization strategies, which is a key part of management in these patients. Additional imaging is often dictated by the surgical team and is beyond the scope of this document but can include, from least to most invasive, duplex ultrasound, cardiac computed tomography angiography, and angiography.

MANAGEMENT BASED ON WIFI CLASSIFICATION

Wound

Tissue Characteristics

When wound healing stalls, the wound is no longer acute and enters a chronic state that does not proceed through the typical phases of healing due to dysregulation of signaling networks that control timely cellular and tissue responses. For instance, the epidermis is hyperproliferative, but not migratory, there is marked decrease of angiogenesis, dysregulation of matrix deposition and its turnover, and a delayed inflammatory immune cell response followed by a compensatory increase in inflammation. All of these issues, compounded by the underlying presence of neuropathy, and likely PAD, contribute to the nonhealing wound phenotype.[72] As a result of all these complex deregulated processes, wounds persist in a chronic, yet ineffective, inflammatory state that does not approach the quantity or quality of inflammatory response seen in acute wounds, leading to a failure of progression through the usual stages to complete wound healing.[73] This concept was confirmed

by the recent spatial transcriptomics analyses of healing and nonhealing DFUs that showed increasing inflammatory macrophage polarization in healing DFUs and specific fibroblast phenotype enriched in healing DFUs,[60] thus revealing cell type–specific targets for potential therapeutic intervention. In addition, chronic wounds are considered colonized by bacteria, due to the frequent presence of aggregates of microorganisms and bacterial biofilms that further impede healing.[74] At present, a major therapeutic goal is to shift this chronic, nonhealing cellular phenotype into one that more closely resembles that of a normal, acutely healing wound.

Debridement

One of the mainstays of standard care for DFU that allows the wound to reset on the path of acute healing is debridement. Although often designated as wound bed preparation, this term is something of a misconception because debridement must extend to the wound edges to remove the hyperproliferative nonmigratory epidermal edge to be successful. Studies have shown that cells grown from postdebridement tissue biopsies show significant improvement in migratory capacity, reconstituting growth factor receptors and signaling networks, resulting in a better response to growth factors.[75] As mentioned previously, biofilms likely exist on most wounds. A biofilm is a thin layer of microorganisms that adheres to a surface and often produces a slimy film of extracellular matrix that can be composed of DNA, proteins, and polysaccharides. Sharp debridement also temporarily removes biofilm and resultant bioburden. Although bacterial growth resumes postdebridement, this procedure allows for a more diverse microbiome, which has been associated with better healing outcomes.[74,76,77]

Offloading

In addition to good-quality debridement, offloading normal (vertical) and shear (horizontal) stress is essential in both reversing the pathogenic process of nonhealing and in creating a protected environment to allow healing. A number of promising therapies exist to offload and protect the healing wound.[78] The tool with the most consistent data is the total contact cast,[79] applied with minimal padding and designed to spread out force over a large unit area. Unfortunately, few (2%–15%) specialty clinics use this tool as a primary means of offloading.[80] There are a number of removable cast walkers that also reduce pressure as well as the total contact cast but do not result in better or even equivocal healing in randomized controlled trials. This is ostensibly because patients often remove these devices and, due to underlying neuropathy, go on to experience repetitive trauma to the area. In fact, data suggest that, unfortunately, these removable devices are worn for <30% of total daily activity.[81] Clinicians have taken these data and modified the removable devices to make them irremovable, which has dramatically increased their efficacy.[82] As our collective population becomes increasingly neuroischemic (rather than classically neuropathic), many centers use a hybrid of removable and irremovable strategies depending on the function, work status, and activity of a patient. Newer therapies are now focusing on providing real-time feedback to the patient and clinician to improve adherence to offloading.[83] Several types of offloading footwear are shown in Figure 4.

Dressings

Many foot ulcers in people with diabetes produce little exudative drainage, particularly those with an underlying ischemic component. Thus, dressings used to treat such wounds should prioritize moisture donation to the wound bed. Hydrogel dressings are a good example of dressings that provide additional moisture to the wound environment and are a good choice in this situation. Wounds with more drainage are best treated with alginates or hydrofibers that have a larger capacity to remove moisture. Aiming to use dressings that maximize the interval between dressing changes to permit irremovable offloading is optimal. A list of currently used dressings and their respective characteristics are displayed in Table 1.

Biologics

Advanced biologic therapies that are currently Food and Drug Administration–approved for efficacy in DFUs include growth factor and living cell–based products. These therapies may achieve tissue reprogramming and reactivation of an acute wound phenotype.[84] Many advanced biologic therapies fail to show efficacy due to multiple reasons, including lack of adequate models for preclinical testing, lack of patients' tissue for analyses, and single acceptable primary outcomes, to name a few.[72] It is remarkable that no small molecules have crossed the threshold of approval. Variability in efficacy of the current biologics reflects lack of ability to phenotype wounds on a more granular level that would allow for more precise targeting. For example, topical application of a growth factor will be efficient only in a subset of patients whose wound cells appropriately express the membranous receptor for that particular growth factor, further emphasizing the need for personalized medicine in this space.

Prevention of Ulcers and Recurrence

Although there are insufficient data to guide clinicians on primary prevention of DFUs, data suggest that several interventions, including podiatric care, self-assessment with thermometry, directed surgical intervention to reduce deformity, and therapeutic footwear, may promote reduction in risk for recurrence for patients in DFU remission.[13,85–89] Self-examination is an important part of prevention of DFUs and management of patients with DFUs. Patients with diabetes should be advised to regularly check their feet for cuts, blisters, redness, swelling, and other signs of injury. They should also be advised to check for numbness or a loss of feeling in

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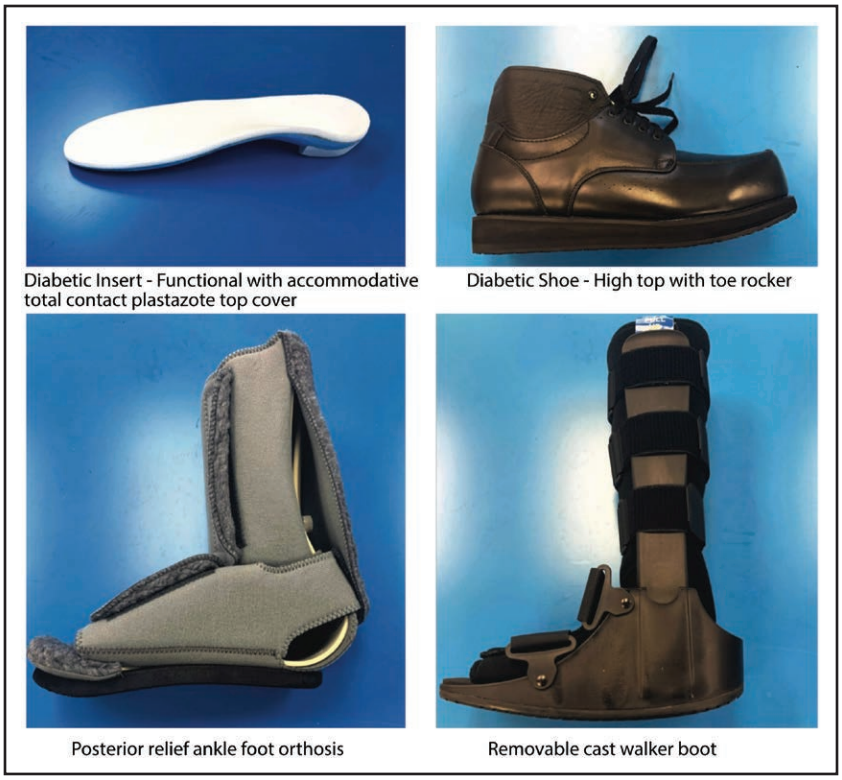

Figure 4. Representative images of diabetic footwear.

their feet, because neuropathy can make it difficult to sense a break in the skin. It is recommended that patients with diabetes see a podiatrist to assist with pressure offloading as a preventive measure.

Ischemia

Diabetes is associated with an increase in both the incidence and severity of PAD, as well as differences in anatomic disease distribution compared with patients who have PAD without diabetes.[90,91] Concomitant diabetes and PAD pose a grave threat to life and limb, where patients with both disease processes have a risk of limb loss that is 4 times the national average.[92,93] Hence, evidence-based, effective revascularization represents a critical component of limb salvage in patients with DFUs.

Revascularization in the diabetic patient with severe PAD (CLTI) presents specific, unique clinical challenges. Restoration of in-line flow to the foot, in general, is considered a requisite to resolve tissue loss. Patients with diabetes and CLTI frequently have multilevel arterial occlusive disease with a high incidence of deep femoral artery, infrapopliteal, and sometimes pedal disease. At present, there are multiple available revascularization techniques; however, there is a paucity of high-quality data to guide effective revascularization strategies. The BASIL trial (Bypass Versus Angioplasty in Severe Ischaemia of the Leg) directly compared bypass with endovascular strategy in patients with CLTI. These authors demonstrated no difference in amputation-free survival between patients with CLTI who underwent bypass versus angioplasty.[94] However, patients in the BASIL trial randomly assigned to open surgery, who survived for ≥2 years, appeared to have improved outcomes. Since the completion of this landmark study, endovascular techniques have greatly expanded. The National Institutes of Health–sponsored BEST-CLI trial (Best Endovascular Versus Best Surgical Therapy for Patients With Critical Limb Ischemia) was designed to address this question in a contemporary fashion.[95] The primary outcomes of BEST-CLI demonstrate that, among patients with CLTI who were deemed suitable for either open bypass or endovascular intervention, and who had an adequate great saphenous vein available for conduit, initial treatment with surgical bypass was associated with a significantly reduced incidence of major limb amputation or major reinterventions, with no difference in all-cause death. The BEST-CLI trial population (N=1830) included 72% with diabetes and 80% with tissue loss, so its results are highly relevant.[96] Further data from this landmark trial, including quality of life, cost-effectiveness, and anatomic complexity of disease, are highly awaited.

In everyday practice, revascularization decisions in diabetic patients with CLTI are heavily influenced by the fragility of the patient, the concomitant degree of tissue loss and infection (limb severity), and the anatomic complexity of disease encountered.[11] These decisions are complex and often require shared decision-making between patient and physician. As noted above, effective treatment for CLTI often requires dealing with multilevel occlusive disease. The following subsections summarize treatment options based on anatomic level.

Table 1. Dressing Categories and Properties

Dressing category	Characteristics	Examples
Alginates	Forms moist gel as it absorbs: requires a secondary dressing	Algisite
	Conformable or fills dead space	Kaltostat
	Manages moderate to heavy exudate	Maxorb
	Can be combined with antimicrobials	Melgisorb
Collagens	Bovine-, equine-, porcine-, or avian-derived products that assist in stimulating wound progression	Fibracol
	Multiple forms: gel, pad, paste, powder, sheets	Promogran
	Some dissolve completely and others will need to be removed (check manufacturer guidelines)	Biostep
	Usually requires a secondary dressing	Triple Helix Collagen Dressing
	Should not be used on infected wounds	…
Composites	Combine different dressing functions into one product (ie, antimicrobial, absorption, adhesion)	Covaderm Plus
		DermaDress
		Leukomed
		Mepore
Foams	Absorb moderate amounts of exudate	Biatain
	Can be used under compression	Optifoam
		PolyMem
		Mepilex
Gauze	Highly permeable	Curity
	Appropriate for wound cleansing, as a cover dressing and for dressing securement	Kerlix
	Not appropriate as a primary wound dressing	Kling
		Packing strips
Hydrocolloids	Impermeable to bacteria	Comfeel
	Facilitates autolytic debridement: do not use on infected wounds	Duoderm
	May tear fragile skin	Exuderm
		Replicare
Hydrogels	Glycerin and water-based products available as amorphous gels, sheets, or impregnated dressings	…
	May be antimicrobial	Duoderm gel
	Donates moisture to wounds	Elasto-gel
	Can assist in autolytic debridement	Intrasite
	May reduce pain	Solosite
	Requires secondary dressing	…
Super absorbents	Absorb large amounts of exudate	ConvaMax
	Fluid lock technology similar to diapers	Drawtex
	Available in different dressing sizes and rolls	Drawtex edema wrap
	Some products may become bulky as they absorb more exudate	…

Aortoiliac

Many aortoiliac lesions are amendable to endovascular treatment. The primary endovascular strategy remains balloon angioplasty and stent placement; balloon-expandable (bare metal versus covered) stents are preferred for the common iliac artery, whereas self-expanding stents are preferentially used for external iliac artery lesions. The results of endovascular therapy are durable, with 5-year patency >80%.[97] Open surgical reconstructions are typically reserved for failed endovascular interventions, small-caliber vessels, and long-segment occlusive lesions, particularly when bilateral.[98]

Common Femoral and Femoropopliteal

Common femoral endarterectomy with patch angioplasty remains the gold standard approach for common femoral lesions. Endarterectomy couples low perioperative morbidity with excellent long-term durability.[99,100] Although there is growing enthusiasm in the interventional realm for endovascular approaches to the common femoral artery, the reality of jeopardizing blood flow to the profunda artery, which is often an important lifeline for diabetic patients to maintain perfusion and avoid limb loss, and the potential need for additional procedures in the future, as well, should be carefully considered before proceeding with such interventions.[101–103]

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Femoropopliteal lesions may be treated with either endovascular or open approaches. Endovascular options include transluminal percutaneous angioplasty, antiproliferative therapies, such as drug-coated balloons and drug-eluting stents, debulking techniques such as atherectomy, and novel treatments for calcium such as intravascular lithotripsy. Endovascular therapies carry a low periprocedural morbidity and mortality; however, the primary patency is variable owing to the diversity of techniques and spectrum of anatomic lesions encountered, and the lack of longer term follow-up for many of the newer techniques, as well.[104–106] Factors such as longer lesion length, smaller vessel diameter, extensive calcification, and runoff disease predict worse outcomes. Femoropopliteal bypass remains an effective treatment option for patients with extensive disease. Results are heavily dependent on the availability of suitable autologous conduit. Saphenous vein bypasses result in a 5-year patency of 65% to 75%, whereas prosthetic bypass yields 30% to 60% patency.[107,108]

Tibiopedal

Tibiopedal disease is particularly prevalent in patients with diabetes and especially those with DFUs. The durability of tibial endovascular interventions remains a significant challenge primarily because there is a scarcity of tools available to effectively treat long, calcium-laden lesions in small-caliber arteries. The primary endovascular approach for tibial disease is percutaneous angioplasty; the 1-year patency is between 40% and 60% but is significantly lower for longer and more calcified lesions.[109,110] Similar to femoropopliteal disease, femorotibial bypass remains a durable option for patients with suitable autologous conduit and an adequate target vessel.[111]

The global epidemic of diabetes, especially with concomitant chronic renal disease, has prompted growing interest in the reconstruction of pedal arteries. Surgical bypass to below ankle arteries is a well-described and effective technique in appropriately selected patients.[112] Interventional techniques at this level have gained growing interest but their effectiveness remains unclear. The Rendezvous registry demonstrated in 257 patients with CLTI that pedal artery angioplasty improved wound-healing rates.[113] However, this was a retrospective study and there remains a paucity of robust, prospective data. Other new techniques of interest for challenging tibiopedal disease include intravascular lithotripsy and deep venous arterialization, but their roles at present are not clear.[114]

Infection

The genesis and resolution of a DFU-related infection is primarily a clinical diagnosis. The presence of bacteria in the wound does not by itself indicate active infection because microorganisms colonize all wounds. Soft tissue erythema, wound size, depth, associated drainage, and tissue and bone exposure should all be evaluated during the initial assessment. These signs may not be as obvious in a patient with diabetes, and this is particularly true in patients with neuropathy, who may not have the painful feedback that might prompt one to seek prompt care. Thus, it can be difficult to diagnose DFU-associated infection solely on the basis of a patient's subjective history or symptoms. A thorough examination by an experienced clinician is, therefore, important. Infection in patients presenting with DFU is often missed or its severity underestimated. Mild (superficial and limited in size and depth), moderate (deeper or more extensive), or severe infections (accompanied by systemic signs or metabolic perturbations) should be classified according to evidence-based guidelines. Patients with active acute infections require special attention and focused care. All patients with DFU infections require basic blood testing that includes a complete blood count, serum chemistries, and inflammatory markers (erythrocyte sedimentation rate and C-reactive protein). The Systemic Inflammatory Response Score is used to determine the overall grade of infection, with 1 point awarded for each of the following potential findings:

- Temperatures >38 °C or <36 °C
- Heart rate >90 beats per minute
- Respiratory rate >20 breaths per minute; or $Paco_2$ >32 mm Hg
- White blood cell count >12 000, 4000 cells/L, or 10% immature (band) form

Patients with a Systemic Inflammatory Response Score of ≥2 require more immediate resuscitation and the administration of intravenous antibiotics. For example, patients that meet Systemic Inflammatory Response Score criteria with a WIfI Foot Infection grade 3 require more intensive medical and surgical intervention than those with lower infection grades. It is also critical to treat any associated hyperglycemia and other electrolyte or metabolic derangements that could accompany infection. Last, hyperglycemia of an unexplained cause should be thoroughly investigated because it may portend underlying infection. Blood and deep tissue cultures (obtained during debridement) can aid in the selection of appropriate antibiotics. Although superficial swab cultures are frequently obtained in these patients, they are not recommended because their utility is limited because most wounds are contaminated by superficial skin flora, which does not always identify the organism responsible for the infection. After deep tissue cultures are obtained, therapy consisting of empiric antibiotics should be initiated. Once bacterial speciation and drug sensitivities become available, the antibiotics should be narrowed down as much as possible. Proper antibiotic selection is not only important for treating active infection, but it can also slow the spread of antimicrobial resistance. Topical antimicrobials, although used frequently, have not, to

date, shown any benefit in reducing severity of infection. Infectious disease experts are often part of the multidisciplinary DFU management team at specialized centers given the importance of infection treatment in these patients.

The Infectious Diseases Society of America and International Working Group on the Diabetic Foot have published detailed recommendations on empiric treatment on the basis of the severity of the infection and the suspected organism. Intravenous antibiotics are usually reserved for infections severe enough to necessitate hospitalization, although some specialized outpatient and infusion centers may provide such care. Undrained purulence and nonviable tissue should be surgically debrided as soon as possible. In general, addressing infection should take precedence over any attempts at revascularization. However, close communication with vascular specialists as part of a multidisciplinary limb preservation team is critical for avoiding any potential delays in care once source control of the infection has been obtained.

Infection Involving Bone

If it is possible to probe the bone through the ulcer, the likelihood of bone infection increases significantly. As discussed above, imaging involving plain radiographs, and MRI and other modalities, as well, are often necessary to determine the degree of infection and bone involvement. If osteomyelitis is present, bone debridement and prolonged intravenous antibiotics will most likely be required to allow wound healing, even in patients that do not require revascularization. A definitive diagnosis of osteomyelitis can be obtained with bone biopsy and deep bone culture. For cases in which bone biopsy is not an option, deep wound cultures may provide a reasonable alternative to diagnose infection and direct antibiotic therapy.

Patients with DFU infection involving bone may ultimately require definitive surgical treatment to eradicate the infection. In these cases, all devitalized tissue and bone should be surgically removed. Soft tissue and partial bone excision may be sufficient in some cases, but in many cases, particularly involving forefoot osteomyelitis, trans-metatarsal amputation or pan-metatarsal head excision may be required. Furthermore, multiple debridements and drainage procedures may be required to completely eradicate deep infection; in severe limb- and life-threatening cases, foot functionality may be sacrificed to clear the infection with the hope of eventually achieving wound closure and surgical reconstruction once the infection is resolved. Recent evidence also suggests that suppressive antimicrobial therapy may be clinically effective for some patients; however, this is presently under further investigation.[115]

A management algorithm in a patient presenting with a new DFU is detailed in Figure 5.

SPECIAL CONSIDERATIONS IN THE DIABETIC, CARDIOVASCULAR POPULATION

Despite significant scientific and clinical advances, cardiovascular sequelae, such as myocardial infarction, stroke, and major amputation, remain a recalcitrant problem for patients with diabetes. Hence, there is a critical need to delineate the myriad of cardiovascular phenotypes observed in diabetic patients and to develop novel strategies to risk-stratify this cohort. An emerging risk-stratification approach for cardiovascular patients is to consider the presence of polyvascular disease. Although the specific patterns of PAD that occur in patients with diabetes are discussed above, it is important to note that polyvascular disease is the presence of atherosclerosis in ≥2 arterial beds, and it is associated with increased risk for major adverse cardiovascular events (MACE).[116] Diabetes and polyvascular disease often coexist, and concurrence represents an additive and synergistic cardiovascular risk.[117]

For example, the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Results) randomly assigned 9320 patients with type 2 diabetes to liraglutide, a glucagon-like peptide 1 analogue or placebo. A post hoc analysis of this trial demonstrated that, at a median follow-up of 3.8 years, the rate of MACE was 22% in the polyvascular cohort compared with 15% in the nonpolyvascular group (hazard ratio, 1.52 [95% CI, 1.33–1.72]).[118] In addition, the SAVOR-TIMI 53 trial (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus) demonstrated that an increase in MACE rate was associated with an increase in arterial bed involvement: single bed (7.5%), 2 bed (15.6%), and 3 bed (23.9%; $P<0.0001$).[119] The current body of evidence strongly suggests that the coexistence of diabetes and polyvascular disease represents a high-risk cardiovascular population. No randomized trials have been conducted to specifically address the management of this high-risk cohort. However, there is emerging evidence that the intensification of lipid-lowering agents, antithrombotic and antiplatelet therapies, may improve clinical outcomes in this vulnerable population, and these guidelines should direct medical management in patients who have DFUs with cardiovascular disease. Important details regarding the major recent trials that have examined medical therapy in the setting of cardiovascular disease are shown in Table 2.[120–127]

Medical Management in Patients With DFUs With Cardiovascular Disease

Lipid-lowering therapies remain a cornerstone of cardiovascular care; hence, there is great interest in exploring the benefits of intensive lipid-lowering therapies for high-risk populations. In a post hoc analysis of IMPROVE-IT

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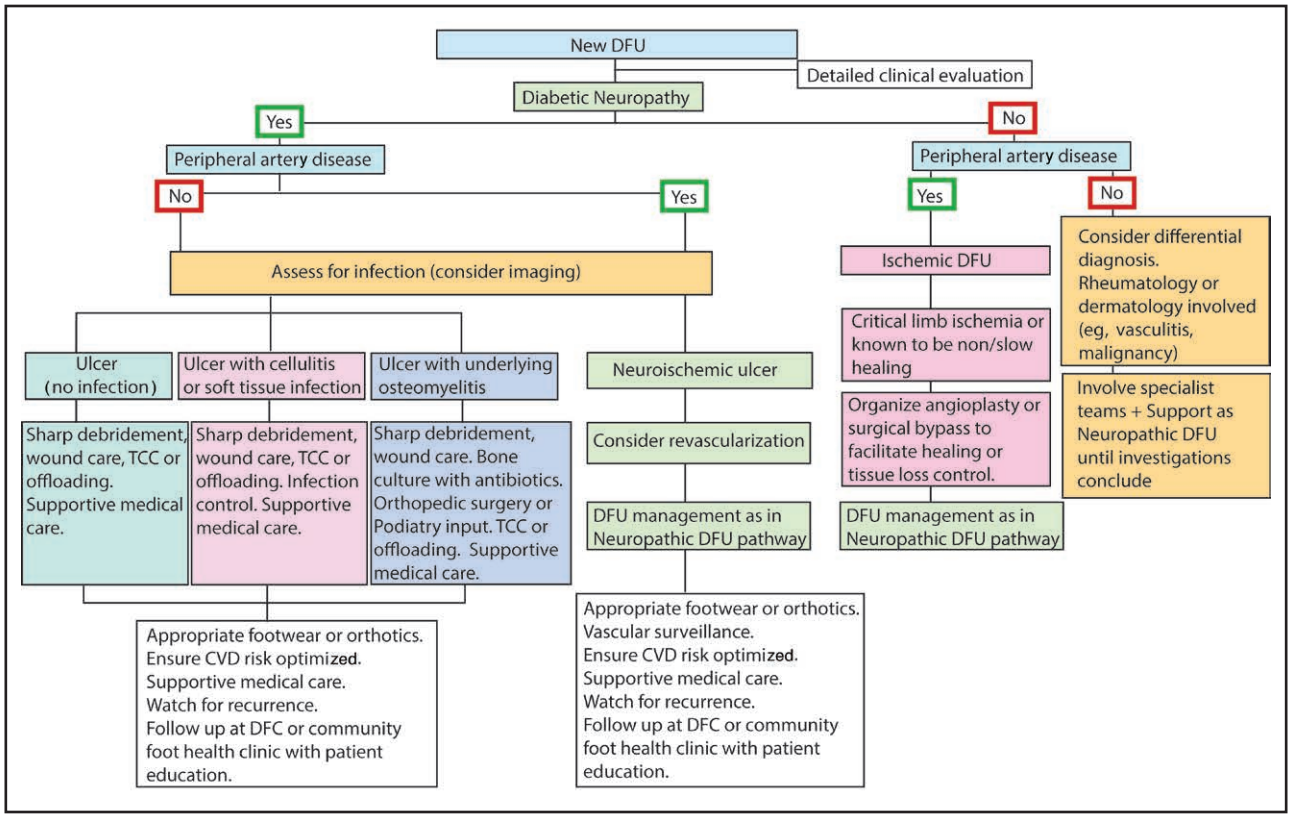

Figure 5. Algorithm for evaluation of new DFUs.
CVD indicates cardiovascular disease; DFU, diabetic foot ulcer; and TCC, total contact cast.

(Improved Reduction of Outcomes: Vytorin Efficacy International Trial), a randomized, placebo-controlled study evaluating the addition of ezetimibe to statin therapy in patients with a recent acute coronary syndrome, the investigators demonstrated that patients with polyvascular disease and diabetes had significantly higher cardiovascular events compared with either subgroup alone. Furthermore, they show that intensive lipid-lowering therapies resulted in absolute risk reduction of 9% over 7 years in patients with both type 2 diabetes and polyvascular disease.[128] Moreover, the development of PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors has further enhanced our ability to inhibit lipid-related cardiovascular sequelae. In fact, PCKS9 inhibitors have demonstrated clinical efficacy in patients with polyvascular disease, and their use has been incorporated into recent societal guidelines.[129] In the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk), treatment of patients who have PAD with a PCSK9 inhibitor significantly reduced major amputation and acute limb ischemia events.[130] Although not specific to patients with PAD with DFUs, these guidelines can be broadly interpreted to have benefit in this population given their beneficial effects in patients with polyvascular disease.

Thrombin generation is a key event in the pathophysiology of ischemic events, such as acute coronary syndrome, stroke, and CLTI. Historically, thrombin-inhibition therapies have demonstrated limited clinical utility and unacceptable bleeding risk. The advent of factor Xa inhibitors has reinvigorated interest in antithrombotic strategies for cardiovascular risk reduction. The COMPASS trial (Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease) evaluated the efficacy of (1) rivaroxaban alone, (2) rivaroxaban in combination with aspirin, and (3) aspirin alone for secondary cardiovascular prevention. The study randomly assigned >27 000 patients with stable atherosclerotic vascular disease to the 3 regimens. At a mean follow-up of 23 months, the authors demonstrated that low-dose rivaroxaban plus aspirin resulted in a 24% reduction in MACE compared with aspirin alone. Diabetic patients represented 44% of the study cohort in COMPASS and the reduction in MACE with rivaroxaban and aspirin was similar between diabetic patients and nondiabetic patients.[120] Furthermore, the VOYAGER PAD study (Vascular Outcomes Study of ASA [Acetylsalicylic Acid] Along With Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD), showed that a combination of aspirin and rivaroxaban reduced both MACE and major adverse limb events in patients with PAD undergoing endovascular or surgical revascularization.[131] As the aforementioned studies demonstrate, thrombin inhibition through factor Xa inhibitors is an effective tool

Table 2. Medical Therapy Trials Applicable to Cardiovascular Patients With DFUs

Medica strategy	Intervention	Trial	Study population	Results
Antithrombotic	Rivaroxaban	COMPASS[120]	27 395 patients with stable atherosclerotic disease randomly assigned to rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg daily)	Primary outcome, a composite of cardiovascular death, stroke, or myocardial infarction, occurred less frequently in the rivaroxaban/aspirin group, compared with the aspirin alone group
	Rivaroxaban	VOYAGER[121]	6564 patients with PAD who had undergone revascularization were randomly assigned to rivaroxaban (2.5 mg twice daily) plus aspirin or placebo and aspirin	Patients in the rivaroxaban and aspirin cohort had a significantly lower incidence of acute limb ischemia, major amputation, myocardial infarction, ischemic stroke, or death from cardiovascular causes than patients taking aspirin alone
Antiplatelet	Aspirin	Antithrombotic Trialist Collaboration[122]	Collaborative meta-analysis, including 287 studies with 135 000 patients, comparing antiplatelet therapy vs control	Low-dose aspirin was protective against serious cardiovascular events
	Clopidogrel	CAPRIE[123]	19 185 patients with atherosclerotic vascular disease were randomly assigned to clopidogrel (75 mg daily) vs aspirin (325 mg daily)	Clopidogrel was more effective in reducing cardiovascular events than aspirin
	Ticagrelor	EUCLID[124]	13 885 patients with symptomatic PAD were randomly assigned to ticagrelor (90 mg twice daily) or clopidogrel (75 mg daily)	In patients with symptomatic PAD, there was no difference in cardiovascular events between ticagrelor or clopidogrel
Lipid lowering	Statin	Heart Protection Study[125]	6748 patients with PAD and 13 788 high-risk patients were randomly assigned to simvastatin (40 mg daily) or placebo	In patients with PAD, simvastatin reduced major vascular events
	Ezetimibe	IMPROVE-IT[126]	18 144 patients with a recent acute coronary syndrome were randomly assigned to simvastatin (40 mg) and ezetimibe (10 mg) or simvastatin (40 mg) alone	Statin/ezetimibe combination therapy resulted in improved cardiovascular outcomes
	PCSK9 inhibitors	FOURIER[127]	27 564 patients with atherosclerotic cardiovascular disease and already prescribed a statin were randomly assigned to evolocumab (either 140 mg every 2 wk or 420 mg monthly) or placebo	Evolocumab (PCSK9 inhibitor) in addition to statin therapy reduced cardiovascular events

CAPRIE indicates Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events; COMPASS, Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease; EUCLID, A Study Comparing Cardiovascular Effects of Ticagrelor and Clopidogrel in Patients With Peripheral Artery Disease; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; PAD, peripheral artery disease; PCSK9, proprotein convertase subtilisin/kexin type 9; and VOYAGER PAD, Vascular Outcomes Study of ASA (Acetylsalicylic Acid) Along With Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD.

to mitigate ischemic events in cardiovascular patients. However, the benefit of antithrombotic therapy for diabetic patients has yet to be evaluated in a prospective fashion. For future secondary risk reduction trials, it will be imperative to intentionally include patients with diabetes and polyvascular disease to accurately determine the clinical efficacy of these therapies.

MULTIDISCIPLINARY MANAGEMENT

The presence of DFUs in cardiovascular patients represents a complex clinical dilemma. It requires the comanagement of many interrelated clinical issues, including neuropathy, bony abnormalities (such as Charcot foot) and infections, soft tissue, PAD, and tissue loss. This is in addition to the complex medical management required in these patients to decrease hyperglycemia and concomitant other cardiovascular diseases (ie, hypertension, hyperlipidemia). No single health care professional or specialty possesses the requisite skill set to manage all the facets of this complex clinical problem. Hence, multidisciplinary teams are an essential part of providing high-quality care to this patient population. The tenets of multidisciplinary management of these patients are detailed in Supplemental Table 2.[132]

Team-based approaches have been demonstrated to significantly improve DFU care and limb salvage rates in a wide variety of clinical settings.[133] Effective team management requires (1) acquisition of the requisite health care professionals, (2) a well-defined team structure, (3) adherence to evidence-based guidelines, (4) an infrastructure for robust data collection, and (5) mechanisms for quality improvement on the basis of the review of clinical outcomes.

A strong understanding of the natural history and potential complications of DFUs should guide the formation of an effective team. In the recently published global vascular guidelines, Conte et al[134] outlines 9 essential skill areas required to create an effective diabetic foot team. The 9 required skills areas include the following: (1) hemodynamic and anatomic vascular assessment; (2) peripheral neuropathy workup; (3) obtaining site-specific cultures; (4) WIfI staging; (5) incision, drainage, and debridement of wounds; (6) delivery of culture-specific

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antibiotic therapy; (7) revascularization; (8) soft tissue and bony reconstruction for foot deformities; and (9) postoperative surveillance to limit the risk of recurrent ulceration.

Given the inherent diversity in the clinical skillset required for the formation of an effective diabetic foot team, effective communication is paramount. In a systemic review focusing on the composition and efficacy of multidisciplinary DFU care, Musuuza et al[133] reported that a defined team structure with a primary nuclear team and ancillary team of consultants was a common element among successful larger teams. The nuclear-ancillary team paradigm permits consistency and continuity among a small, dedicated core group while allowing access to the entire complement of required knowledge and clinical expertise.

In addition to establishing a multidisciplinary team with the appropriate individuals and infrastructure, adherence to established clinical guidelines and quality improvement mechanisms are essential. Well-established clinical pathways and algorithms are required to ensure that patients are receiving timely, comprehensive care. However, clinical guidelines are not universally applicable in all clinical settings; they often need to be adapted to best suit the strengths and weaknesses of individual institutions. Hence, it is critical to establish a system for rigorous data collection along with the mechanisms to analyze the collated clinical data and use the information to drive quality improvement.

CURRENT CLINICAL TRIALS FOR DFU IN CARDIOVASCULAR PATIENTS

Data from clinical trials and clinical practice suggest that somewhere between 25% and 50% of patients with DFUs heal between 12 and 20 weeks with high-quality standard care, although patients with significant cardiovascular disease portend a poorer prognosis.[135] The DFUs of patients enrolled in trials were classically neuropathic or neuroischemic ulcers on the plantar aspect of the feet, but more recently the trials have expanded their criteria to include patients with diabetes with any leg or foot ulcer. Therefore, some patients included in the trials may have venous insufficiency–related ulcers or postsurgical ulcers. This heterogeneity might account for varied reported healing rates in many of the DFU trials to date. Although it was previously thought that tight diabetes control can improve DFU healing, only a few reports within a range of reasonable diabetes control (hemoglobin A1C <10%) suggest that diabetes control actually affected DFU healing.[136] Given these issues, there is a significant need for clinical trials data to better understand and identify evidence-based interventions to improve DFU outcomes and time to healing. According to a recent review by the American Diabetes Association, although a multitude of products exist to treat refractory ulcers, only 11 are supported by evidence from randomized control trials. Furthermore, only 4 are Food and Drug Administration approved (Supplemental Table 3),[137] including 1 drug and 3 cell and tissue-based products. As of April 2022, 30 interventional trials are listed in clinicaltrials.gov as actively enrolling in phase 1 to 3 trials. These include products aimed at improving tissue repair, interventions aimed at treating infection, and interventions aimed at improving blood supply. These low numbers of ongoing trials further reinforce the need for more translational research on DFUs.

Most trials are currently designed to address 1 of 3 major areas of dysfunction: wound cellular dysfunction, infection, or ischemia. Although several drugs, products, or other interventions may work through multiple pathways, interventions whose major mechanism of action is aimed at improving cellular dysfunction and tissue repair include novel cell- and tissue-based products, electrical stimulation, products aimed at improving offloading adherence, traditional and small molecules such as folic acid or those targeting β-adrenergic receptors, among others. Drugs, products, and interventions aimed at addressing primarily the ischemic component of nonhealing include nitric oxide, mesenchymal stem cells derived from umbilical cord, adipose tissue, or other sources, gene therapy and growth factor therapy, among others. Last, several interventions under investigation are aimed primarily at treating or preventing infections. These include novel combinations of antibiotics, bacteriophage therapy, and new debridement products.[138,139]

FUTURE RESEARCH DIRECTIONS

The complexity of the wound repair process itself, particularly from molecular, cellular, and physiological perspectives, coupled with the intricacy of diabetic, cardiovascular patients, mandates a multidisciplinary approach both in the clinical setting, as well as in the research realm. Although more sophisticated technologies, such as single-cell or spatial "omics" and big data analytics of artificial intelligence are being used, there are major gaps in all research areas that translate into the absence of effective treatments that are critically needed for this increasing patient population. Current scientific opportunities in this space are listed in Table 3.

Basic and Translational Research

Current basic and translational research is focused on understanding the mechanisms and regulation of various cells in the wound and systemic circulation that control the wound repair process and those that contribute to impaired healing in DFUs.[72] Basic science

Table 3. Future Scientific Directions

Basic science and translational research	Clinical science	Population science
Use of "OMICS" technologies (spatial transcriptomics, single-cell analysis, epigenetic proteomic and lipidomic assessments) to better understand development of the disease and its pathophysiology	Expanding primary outcomes for clinical trials	Disparities (racial, ethnic, gender):
		A. Access to health care
		B. Revascularization vs amputation
		C. Pharmacoequity
		Focus on inclusive representation, with input from affected population members
Development of improved animal model(s) for preclinical testing that correspond to human conditions more accurately	Develop approaches to include real-world evidence in clinical testing	Consider concepts of intersectionality when evaluating populations
Integrative biology, connecting clinical with cellular phenotypes	Development of tools for personalized care	Improve specificity of current race and ethnicity categories (ie, beyond "underrepresented racial and ethnic groups," "Hispanic/Latino")
Artificial intelligence and big data analytics to develop better diagnostics	Develop clinical trial networks for interventional testing	Improve current and build new population-level databases
Developing guidelines for standardizing preclinical testing and its reporting	Validation and clinical testing of new predictive diagnostic tools related to healing outcomes (not vascular?)	Include community engaged research approaches in research designs to improve research relevance and translational potential
Development of human-based disease bioengineered models	Establishing accessible biobanking coupled with electronic medical records	Apply mixed-methods research methodology to assess complex questions related to behaviors, disparities, and outcomes
Cellular reprogramming: induced pluripotent stem cells and other approaches of tissue regeneration	Need for validated quality of life and patient-reported outcomes to specific patients with peripheral artery disease	Standardize terminology and improve specificity when studying rural populations

and translational research in wound repair use multiple animal models ranging from model organisms to mammals. Many of the efforts in this area have focused on addressing impaired angiogenesis and increased inflammation, namely through immune cell dysfunction, in DFUs. For example, stem cells mobilize to wound tissue where they secrete chemokines and growth factors that promote angiogenesis and matrix remodeling, a process that is dysfunctional in DFUs.[140] A recent randomized study found that mesenchymal stem cells from bone marrow isolates improved both healing and blood flow in patients with DFUs compared with mononuclear cells or control treatments.[141,142] Although mesenchymal stem cells are a promising therapy for DFUs and the subject of multiple current clinical trials, they suffer from suboptimal retention in tissues, making their utility more limited. Likely engineering therapies designed to deliver these cells and retain them in tissues will be needed to increase their efficacy. Furthermore, epigenetic marks, such as microRNAs and histone methyltransferases, have shown promise in DFUs as biomarkers and therapeutics. Despite some advances with epigenetic therapy, challenges remain, such as potential off-target effects and a need for local cell-specific delivery mechanisms before development of a clinically feasible therapy.[143]

Although this basic work greatly advances our understanding of the molecular and cellular processes that guide wound healing, they often translate poorly to human disease.[144] In contrast, there is often a scarcity of patient samples due to the need for immediate and complex tissue processing, and the capacity to perform mechanistic studies in human specimens is often limited.[145] In addition, lack of adequate animal model(s) for preclinical testing has, to date, resulted in limited therapeutic advances. On the other hand, clinical research is facing multiple challenges as well. Limited by a single Food and Drug Administration–acceptable primary outcome, complete closure, many promising therapeutics never reach the patient bedside. Improving quality of life, reducing pain, recurrence, or amputations, improving mobility, reduction of infection, although highly significant and important from a clinical standpoint, are not acceptable outcomes when it comes to efficacy approval for the purposes of a clinical trial.[146] Furthermore, the challenges of developing treatments for this multifactorial complex disease necessitate a combinatorial or sequential treatment approach. However, costs of trials for multiple treatment arms are often prohibitive. In addition, targeted therapies require stringent inclusion criteria for clinical trials, which yields 2 major problems: slow recruitment and lack of real-world evidence. Taken together, despite scientific discoveries and technologies that are advancing knowledge, there is a major gap in implementing it into effective therapies. Likewise, the diagnostic tools that can be clinically used to improve clinical care are also lacking.[147] Therefore, the research needs will continue to harness advanced technologies focusing on translational aspects of discoveries and their applicable relevance to patients' pathophysiology, development of improved models, and standardized preclinical testing that can yield more effective therapies.

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In turn, this will also result in the development of diagnostic tools and clinical biomarkers that will guide clinical practice to improve clinical outcomes. Furthermore, a concerted effort from the wound-healing community should continue to research and provide even more clinical evidence to support acceptance of clinically justified primary outcomes beyond complete closure.

Population Outcomes and Health Disparities

A number of opportunities remain for further research into DFUs and, hence, amputation-related disparities. This includes research with a deliberate focus on race and ethnicity beyond the general "underrepresented racial and ethnic groups" and overly broad "Hispanic/Latino" category, which currently comprises the majority of research on the subject. This includes research in other racial and ethnic groups, such as Asian American (again, with the hopes of shedding light on specific groups rather than "Asian individuals" as a whole), sex-based disparities, rural-dwelling communities, and disparities faced by LGBTQAI+ communities. Current databases available for large population studies may not offer the level of granularity that is required to truly understand these issues, and, as such, additional data sources need to be built to accurately represent the diverse groups affected by these disparities. It is crucial to include representation from affected communities when building these data sources to conduct rigorous and meaningful research on the subject.

In addition to including affected communities in building datasets, it is crucial that we continue efforts to empower patients and stakeholders to have a seat at the table throughout the research process, with a focus on patient-centered outcomes. Patient-centered outcomes research is critical to ensure that research questions are meaningful, that evidence will be translatable, and that results are disseminated directly to patients and stakeholders. By including patients and stakeholders as active participants in the research process, patient-centered outcomes research has the added benefit of educating patient populations on the best approaches to treat their disease process and improves patient capacity to participate in medical decision-making.

Another focus area for future amputation research is on the use of mixed-methods research approaches to better understand this complicated issue. The overwhelming majority of research on the topic of amputation disparities is quantitative in nature, and although these studies have been useful in identifying the existence and magnitude of amputation disparities, they have significant difficulty explaining why they happen. Qualitative methods are ideal for answering the "why," because they provide essential information about the actual experiences of patients and health care professional dealing with amputation.[148] An integrated mixed-methods approach, which combines both quantitative and qualitative methods, allows for in-depth analysis of complicated problems and is well suited to the complicated issue of amputation.

Last, community-engaged research strategies to address the issues of health disparities related to amputation should be prioritized. As discussed earlier, amputation disparities are complex and deeply rooted in social context. Community partners who can bring their own perspectives and understandings of community life and health issues to a project are crucial for planning and implementing evidenced-based amputation prevention interventions that are feasible, acceptable, and sustainable.[149,150]

ARTICLE INFORMATION

Statement on race and ethnicity and health equity language: The terminology used in this scientific statement is based on the language suggestions of the AHA Structural Racism and Health Equity Language Guide. Update March 2022.

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Katherine A. Gallagher	University of Michigan Surgery Cardiovascular Center	None	None	None	None	None	None	None
Joseph L. Mills	Baylor College of Medicine	None	None	None	None	None	Biogen*	None
David G. Armstrong	Keck School of Medicine of USC Surgery Keck Medical Center of USC	None	None	None	None	None	None	None
Michael S. Conte	University of California, San Francisco	BioGenCell†	None	None	None	None	Angest†; Abbott Vascular*; BioGenCell†	None
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Jorge Plutzky	Brigham and Women's Hospital/ Harvard Medical School	Boehringer Ingelheim (PI, grant investigating improved care delivery)*; Novartis (co-investigator)*	None	None	None	None	Altimmune*; Amgen*; Esperion†; Sanofi*; Novo Nordisk†	None
Kevin W. Southerland	Duke University	None	None	None	None	None	None	None
Marjana Tomic-Canic	University of Miami, Miller School of Medicine	NIH (her research is funded by multiple NIH grants)†	None	None	None	None	Molnlycke*; Flen Health†	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Joshua A. Beckman	University of Texas Southwestern	Novartis (DSMB)*; Bristol Myers Squibb (investigator-initiated grant in pulmonary embolism)†	None	None	None	None	JanOne†; Janssen†	None
Luke Brewster	Emory University/Atlanta VA Health Care System	None	None	None	None	None	None	None
Richard F. Gillum	Howard University	None	None	None	None	None	None	Annals of Epidemiol (assoc editor)*
Naomi M. Hamburg	Boston University School of Medicine	None	None	Sanifit*; NovoNordisk*	None	None	None	None
Clay F. Semenkovich	Washington University	NIH (PI or co-I on grants dealing with PVD and diabetes)†	None	None	None	None	Alnylam*	None

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*Modest.

†Significant.

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