Update of Recently Published AHA Scientific Statement/Guidelines for DFUs in Cardiovascular Patients

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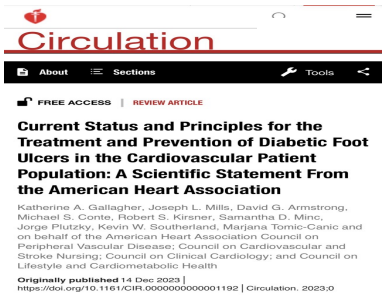
Diabetic Wounds in Cardiovascular Patients


Circulation

About Sections Tools

FREE ACCESS | REVIEW ARTICLE

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, Joseph L. Mills, David G. Armstrong, Michael S. Conte, Robert S. Kirsner, Samantha D. Minc, Jorge Plutzky, Kevin W. Southerland, Marjana Tomic-Canic and 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

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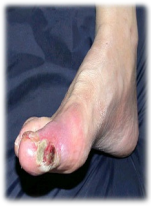
DFU Clinical Relevance

- Economic cost burden: $200 billion dollars/yr – leading cost of hospitalization in diabetics
- ~ 1/3 cost burden related to peripheral wounds
- Impaired wound healing is the leading cause of lower extremity amputation

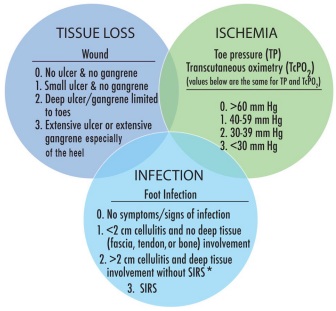


Epidemiology

- Wounds below the malleolus in diabetics
- Lifetime risk of DFU in diabetic is 25-35%
- Presence of DFU doubles mortality


KEEP CALM AND NO SUGAR

Staging

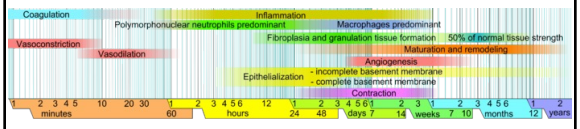


Disparities

- Socioeconomic status, racial, ethnic, geographic status
- Disparities in DFU amputation rates serve as a marker for structural inequities in care/ other social determinants of health

Pathogenesis

Why Do DFU Fail to Heal?

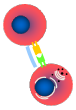


Etiologies for impaired diabetic wound healing

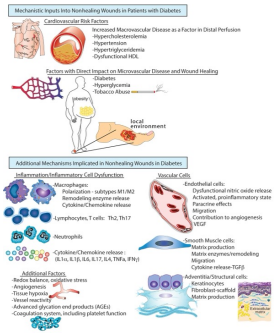
- Ischemia

- Neuropathy

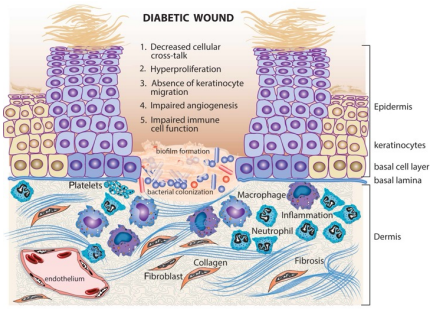
- Impaired immune cell function/inflammation



Macro and Microvascular Disease Associated with DFU

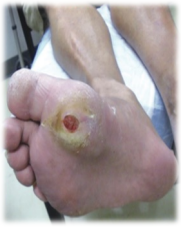


Pathogenesis – Basic Biology



Classification/Treatment: Wound

- **Debridement**
- **Offloading**
- **Dressings/Biologics**



Debridement/Dressings

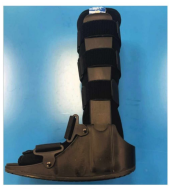
- **Extend to wound edges**
- **Recreate an 'acute' wound**
- **Remove biofilm to increase diverse microbiome**
- **Hydrogel – increase moisture**
- **Alginates – decrease moisture**
- **Growth factors/living cells under evaluation**

Offloading


Diabetic Insert - Functional with accommodative total contact plastazote top cover

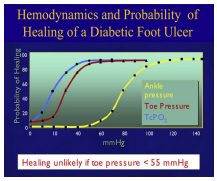

Diabetic Shoe - High top with toe rocker


Posterior relief ankle foot orthosis


Removable cast walker boot

Classification/Treatment: Ischemia

- **BEST-CLI – (72% with diabetes, 80% with tissue loss) – bypass with GSV decrease in amputation**
- **Revascularization based on patient factors, anatomy, infection – shared decision making important**



Classification/Treatment: Infection

- **DFU > 2 weeks – Plain films**
  - **Gas – acute drainage**
- **MRI – chronic bone infections**
  - **If CI – bone scan**
- **No superficial swab**
- **Deep cultures from debridment**

Medical Management

MEDICAL STRATEGY	INTERVENTION	TRIAL	STUDY POPULATION	RESULTS
Anti-Thrombotic	Rivaroxaban	COMPASS[1]	27,395 patients with stable atherosclerotic disease randomized to rivaroxaban (2.5mg twice daily) plus aspirin (100mg 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 to the aspirin alone group
	Rivaroxaban	VOYAGER[2]	6564 PAD patients who had undergone revascularization were randomized 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 on aspirin alone
Anti-Platelet	Aspirin	Antithrombotic Trialist Collaboration[3]	Collaborative meta-analysis including 287 studies with 135,000 patients comparing antiplatelet therapy versus control	Low does aspirin is protective against serious cardiovascular events
	Clopidogrel	CAPRIE[4]	19,185 patients with atherosclerotic vascular disease were randomized to clopidogrel (75 mg daily) versus aspirin (325 mg daily)	Clopidogrel is more effective in reducing cardiovascular events compared to aspirin
	Ticagrelor	EUCLID[5]	13,885 patients with symptomatic PAD were randomized 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[6]	6748 patients with PAD and 13,788 high-risk patients were randomized to simvastatin	In patients with PAD, simvastatin reduces major vascular events
	Ezetimibe	IMPROVE-IT[7]	18,144 patients with a recent acute coronary syndrome were randomized 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[8]	27,564 patients with atherosclerotic cardiovascular disease and already prescribed a statin were randomized to evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or placebo	Evolocumab (PCSK9 inhibitor) in addition to statin therapy reduced cardiovascular events

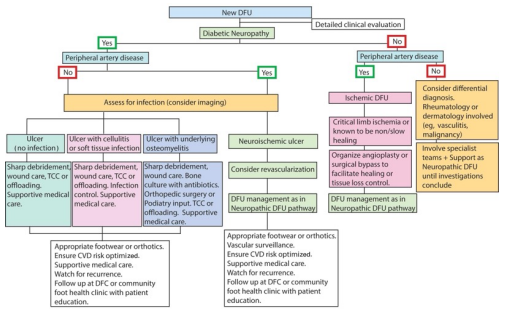
Medical Management

- **IMPROVE-IT – ezetimibe and statin therapy resulted in absolute risk reduction of 9% in diabetic patients ++ major benefit in diabetics**
- **FOURIER – PCSK9 inhibition – PAD patients with reduced amputations**
- **COMPASS – rivaroxaban plus ASA decreased MACE (similar in diabetic vs. non-diabetic)**

Multidisciplinary Care

A team of professionals representing different disciplines to assist in the evaluation and management of the patient with PAD. For the care of patients with CLI, the interdisciplinary care team should include individuals who are skilled in endovascular revascularization, surgical revascularization, wound healing therapies and foot surgery, and medical evaluation and care.
Interdisciplinary care team members may include:
•Vascular medical and surgical specialists (i.e., vascular medicine, vascular surgery, interventional radiology, interventional cardiology)
•Nurses
•Orthopedic surgeons and podiatrists
•Endocrinologists
•Internal medicine specialists
•Infectious disease specialists
•Radiology and vascular imaging specialists
•Physical medicine and rehabilitation clinicians
•Orthotics and prosthetics specialists
•Social workers
•Exercise physiologists
•Physical and occupational therapists
•Nutritionists/dieticians

Algorithm for DFU



Future Directions

Table 4

FUTURE SCIENTIFIC DIRECTIONS		
BASIC SCIENCE AND TRANSLATIONAL RESEARCH	CLINICAL SCIENCE	POPULATION SCIENCE
Utilization of "OMICS" technologies (spacial 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 healthcare B) Re-vascularization vs. amputation C) Pharmacoequity Focuse on inclusive representation - with input from affected populated members
Development of improved animal model(s) for pre-clinical testing that correspond to human condition 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 phenotype	Development of tools for personalized care	Improve spcificity of current race/ethnicity categories (i.e. beyond "non-White","Hispanic/Latino")
AI and big data analytics to develop better diagnostics	Develop clinical trial networks for interventional testing	Improve current/build new population level databases
Developing guidelines for standardizing pre-clinical 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 accesible biobanking coupled with electronic medical record	Apply mixed methods research methodology to assess complex questions related to behavior, disparities and outcomes
Cellular reprogramming - IPSC and other approaches of tissue regeneration	Need for validated quality of life and patient reported out-comes measures specific to PAD patients	Standardize terminology and improve specificity when studying rural popluations

Table 4. Future scientific directions

Acknowledgements

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