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Epidemiology and Risk of Amputation in Patients With Diabetes Mellitus and Peripheral Artery Disease

J. Aaron Barnes, Mark A. Eid, Mark A. Creager, Philip P. Goodney

ABSTRACT: Peripheral artery disease (PAD) stems from atherosclerosis of lower extremity arteries with resultant arterial narrowing or occlusion. The most severe form of PAD is termed chronic limb-threatening ischemia and carries a significant risk of limb loss and cardiovascular mortality. Diabetes mellitus is known to increase the incidence of PAD, accelerate disease progression, and increase disease severity. Patients with concomitant diabetes mellitus and PAD are at high risk for major complications, such as amputation. Despite a decrease in the overall number of amputations performed annually in the United States, amputation rates among those with both diabetes mellitus and PAD have remained stable or even increased in high-risk subgroups. Within this cohort, there is significant regional, racial/ethnic, and socioeconomic variation in amputation risk. Specifically, residents of rural areas, African-American and Native American patients, and those of low socioeconomic status carry the highest risk of amputation. The burden of amputation is severe, with 5-year mortality rates exceeding those of many malignancies. Furthermore, caring for patients with PAD and diabetes mellitus imposes a significant cost to the healthcare system—estimated to range from $84 billion to $380 billion annually. Efforts to improve the quality of care for those with PAD and diabetes mellitus must focus on the subgroups at high risk for amputation and the disparities they face in the receipt of both preventive and interventional cardiovascular care. Better understanding of these social, economic, and structural barriers will prove to be crucial for cardiovascular physicians striving to better care for patients facing this challenging combination of chronic diseases.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: amputation ■ atherosclerosis ■ diabetes mellitus ■ lower extremity ■ peripheral artery disease

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Peripheral artery disease (PAD) is the development of chronic arterial occlusive disease of the lower extremities due to atherosclerosis.[1] PAD is associated with atherosclerosis of other vascular beds, and the presence of diabetes mellitus is known to both increase the incidence of PAD, as well as accelerate disease progression and worsen disease severity.[2] Given this, patients with concomitant diabetes mellitus and PAD are at high risk for ischemic events and subsequent amputation.[3] Furthermore, within this cohort, there is significant regional, racial and ethnic, and socioeconomic variation in the risk of amputation.[3–5] Specifically, residents of rural areas, African-American and Native American patients, and those of low socioeconomic status carry the highest risk of amputation. The purpose of this brief review, therefore, is to describe the epidemiology of diabetes mellitus and PAD in the United States, outline the risk of amputation in the high-risk cohort of patients with concomitant diabetes mellitus and PAD and describe the variation in this risk seen across socioeconomic and racial and ethnic strata.

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Nonstandard Abbreviations and Acronyms

CLTI	chronic limb-threatening ischemia
OR	odds ratio
PAD	peripheral artery disease

Highlights

- Concomitant diagnoses of peripheral artery disease and diabetes mellitus have a negative synergistic effect, leaving patients at a higher risk for amputation than either of the 2 diseases alone.
- Of those with peripheral artery disease, patients of low socioeconomic status, those residing in rural areas, and those of African-American or Native American ethnicity are at the highest risk of amputation
- Over the preceding two decades, the rates of endovascular interventions have risen while inexpensive and evidence-based measures—such as hemoglobin A1c testing—are underused.

EPIDEMIOLOGY OF DIABETES MELLITUS IN THE UNITED STATES

Diabetes mellitus is a disorder stemming from glucose dysregulation. Of those people with diabetes mellitus, 90% to 95% have type 2 diabetes mellitus, whereas 5% to 10% have type 1 diabetes mellitus.[6] Within the United States, >30 million Americans have diabetes mellitus and an additional 84 million Americans meet diagnostic criteria for prediabetes mellitus.[7] This represents >200% increase in disease prevalence over the preceding 2 decades (Figure 1).[7] Meanwhile, the number of incident cases of diabetes mellitus in US adults has decreased each year since 2008 (Figure 1).[8]

Although type 2 diabetes mellitus has historically been a disease diagnosed in adults over the age of 40 years, between 2001 and 2009, there was a 30.5% increase in the overall prevalence of type 2 diabetes mellitus among people <20 years old.[9] In this study, subgroup analysis demonstrated significant increases in the prevalence of diabetes mellitus in both sexes, those ages 10 to 14, and those ages 15 to 19 across the study period. When stratified by race and ethnicity, significant increases in prevalence were seen in white, African-American, and Hispanic youth, but nonsignificant changes in prevalence rates were seen in Asian Pacific Islander and Native American youth. This increase in disease burden among American youth carries important implications regarding the increased risk of early diabetic complications as this cohort transitions into adulthood.[9]

Race, Ethnicity, Regions, and Differences in Diabetes Mellitus

There is significant variation in the prevalence of diabetes mellitus across races and ethnicities in the United States. The lowest prevalence is seen among white adults, where the prevalence of diabetes mellitus is estimated at 7.3% for females and 9.4% for males. Conversely, the rates among African-American adults are estimated at 14.7% and 13.4%, among Hispanic adults 15.1% and 14.1%, and among Asian adults 12.8% and 9.9% for males and females, respectively. The highest prevalence of diabetes mellitus is seen among Native American and Alaska Native adults, with a prevalence of 14.9% and 15.3% for males and females, respectively.[6,10]

A report issued by the Centers for Disease Control in 2016 outlined regional geographic variation in diabetes mellitus prevalence across the United States. The prevalence of total diabetes mellitus across counties within the United States ranged from 1.5% to 33.0% in 2016 according to the Centers for Disease Control.[10] The counties with the highest prevalence were primarily located in the South, along the United States–Mexican border, and in the Midwestern region.[8] This variation and distribution is consistent with prior work documenting trends in US regional variation of diabetes mellitus prevalence between 1999 and 2012.[11]

Diabetes mellitus is a significant risk factor for atherosclerosis within all vascular beds, including PAD, but is also associated with overall cardiovascular disease morbidity and mortality.[2] Cardiovascular disease–associated death rates have been shown to be significantly higher for diabetic patients, largely due to the increased risk of stroke and myocardial infarction, compared with those without diabetes mellitus.[10,12–14] The magnitude of the impact of diabetes mellitus on cardiovascular death varies across studies and models from an 18% increase to a 4-fold increase in mortality.[8,14] Following a myocardial infarction, diabetic patients have higher rates of morbidity, mortality, and repeat infarction than nondiabetic patients.[15–19] A recent systematic literature review found that cardiovascular disease affects 32.2% of patients with type 2 diabetes mellitus and accounts for 50.3% of all deaths in patients with type 2 diabetes mellitus.[20]

EPIDEMIOLOGY OF PAD IN THE UNITED STATES

Peripheral artery disease is defined as chronic arterial occlusive disease of the lower extremities and varies in severity. Although many individuals with PAD are asymptomatic, intermittent claudication is the typical presenting symptom. This is characterized by burning, aching, cramping, fatigue, or numbness in the calves, thighs, or buttocks with ambulation or exercise and is quickly and completely relieved by rest. The most severe manifestation of PAD

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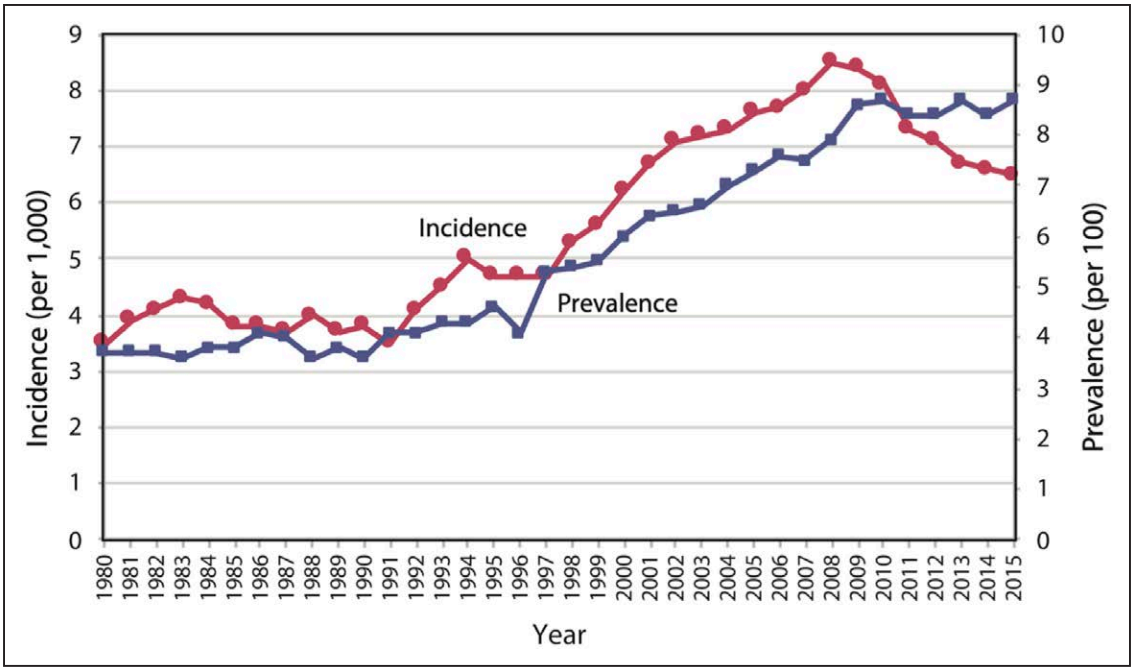

Figure 1. Trends in incidence and prevalence of diagnosed diabetes mellitus among adults aged ≥18 years, United States, 1980–2015.[8]

Note: Rates are age-adjusted to the 2000 US standard population. Data sources: Centers for Disease Control and Prevention, United States Diabetes Surveillance System and National Health Interview Survey.

is termed chronic limb-threatening ischemia (CLTI) and is typified by rest pain or ischemic ulceration or dry gangrene.[21] Ischemic rest pain stems from chronic sensory nerve ischemia and presents as a diffuse burning or aching pain in the forefoot.[1] In many, this pain is worsened with elevation of the extremity and somewhat improved with dependent positioning of the limb. Tissue loss is the development of ulceration, gangrene, or infection in the foot or leg that may ultimately lead to amputation.

Challenges in Measuring the Prevalence of PAD

Accurate epidemiological information on PAD is limited by the fact that only ≈10% of patients with PAD demonstrate the typical symptomology of intermittent claudication.[22,23] This results in a large population with preclinical disease or uncharacteristic symptoms that may not be accounted for. Given this, prevalence estimates have relied on community screening or data on symptomatic patients. Through these approaches, it is estimated that PAD affects between 8.5 and 12 million Americans.[4,24] This prevalence has increased by an estimated 25% over the preceding decade. In high-income countries, such as the United States, prevalence increased by 13.1% between 2000 and 2010. In low- and middle-income countries, prevalence increased by 28.7% over the same time course.[25]

Prevalence of PAD increases significantly with age, such that by age 80 years prevalence is over 20% compared with <5% in those <50 years of age.[26] There is variation in prevalence of PAD across races and ethnicities with African-American patients affected more frequently.[3,4] Specifically, the prevalence of PAD among African-American patients is twice that of non-Hispanic white patients in all age groups. The prevalence of PAD among Hispanics, Asian Americans, and Native Americans is similar to that of non-Hispanic white patients. Investigation into the variation seen across racial and ethnic groupings has demonstrated confounding by education and other socioeconomic variables.[27] This does not discount the variation seen across ethnicities or races but highlights the impact of socioeconomic factors on the prevalence of PAD.

Risk Factors Impacting PAD Prevalence and Progression

In addition to age, significant atherosclerotic risk factors for PAD include cigarette smoking, dyslipidemia, and diabetes mellitus. Cigarette smoking is estimated to double the risk of PAD, although some studies have found smoking to increase the risk of nearly 4-fold.[28,29] Dyslipidemia is estimated to nearly double the risk of PAD.[30] Similarly, diabetes mellitus has been associated with a 2- to 4-fold increase in the prevalence of PAD.[2] Furthermore, smoking, diabetes mellitus, and dyslipidemia have been associated with progression of PAD and worsening lower extremity arterial perfusion.[26,30]

Chronic Limb-Threatening Ischemia

CLTI, the most severe form of PAD, develops in ≈11% of patients with PAD.[1,31] Population studies estimate that the prevalence of CLTI in the US adult population over

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the age of 40 years is 1.28%, which totals ≈2 million individuals.[32] CLTI carries both an elevated risk of amputation and an elevated risk of cardiovascular morbidity and mortality that varies with CLTI severity. A recent systematic review noted 1-year amputation rates ranged from 15% to 20% and 1-year mortality rates ranged from 15% to 40%.[32] The significant variation in amputation and mortality rates can be attributed, in part, to the variation in definitions of CLTI used across studies. To more precisely evaluate the natural history of CLTI, a recent meta-analysis evaluated studies which included only patients with untreated, severe CLTI and found a 1-year major amputation rate of 22% and a 1-year mortality of 22%.[33]

CONCOMITANT DIABETES MELLITUS AND PAD

Diabetes mellitus and PAD independently carry a risk of amputation.[1] The pathophysiology of each is important to understanding the natural history of each disease process and has been the subject of recent reviews.[34,35] Determination of the epidemiology of concomitant diabetes mellitus and PAD faces similar challenges as measurement of disease prevalence in PAD alone. Although the diagnosis of diabetes mellitus is well described, there is broad variability in the severity and symptomology of PAD.[36] Thus, many patients may remain asymptomatic with preclinical disease. As a result, the true prevalence of concomitant PAD and diabetes mellitus is difficult to ascertain. Using best estimates, diabetes mellitus has been associated with a 2- to 4-fold increase in the prevalence of PAD.[2] Of those with PAD, ≈20% to 30% have concomitant diabetes mellitus.[37] Not only does diabetes mellitus result in an increase in the incidence of PAD but it also increases the severity of the disease state.[38] Specifically, patients with diabetes mellitus and PAD more frequently have infrapopliteal or tibial artery disease and vessel calcification compared with nondiabetic patients.[38,39]

RISK OF AMPUTATION IN PATIENTS WITH DIABETES MELLITUS AND PAD

Nearly 100 000 major leg amputations are performed every year in the United States. Of these, over half are attributable to diabetes mellitus and PAD.[40,41] Within the population of PAD patients with CLTI, the estimated prevalence of diabetes mellitus ranges from 27% to 76%.[42] This cohort, with concomitant diabetes mellitus and PAD, carries a risk of amputation that is 4× higher than the national average.[40,41,43,44] Studies have demonstrated that 25% to 90% of amputations within studied populations are associated with diabetes mellitus.[45,46] This risk is thought to be attributable to the combination of peripheral neuropathy and infection stemming from diabetes mellitus and the presence of impaired arterial flow due to PAD. Diabetic ulcers, associated with motor, sensory, and autonomic neuropathy, resultant foot deformities, and impaired wound healing, also are integral to the risk of amputation in patients with diabetes mellitus. Of those with a diabetic ulcer, though, it is estimated that ≈50% have concomitant PAD.[47]

Trends in Overall Amputation Risk Over Time

Despite the increase in the burden of diabetic disease, the overall rate of major amputations in the United States has decreased.[40,41,43,48] Specifically, rates of major lower extremity amputation decreased by 40% between 1996 and 2011 among US Medicare patients.[41,49] This resulted in a major amputation rate of 188 per 100 000 Medicare patients (Figure 2). During this same time period, a shift is observed in revascularization approaches (Figure 2). A 71% decline in the rate of open surgical bypass was observed (201–83 per 100 000) along with an incommensurate increase in the rate of endovascular interventions (138–584 per 100 000).[41] Given the multifaceted and complex natural history of CLTI, it cannot be concluded that the decrease in amputation rates is solely attributable to the shift in revascularization approaches and intensity.[41,49] Concomitant advancements in medical and wound care therapies along with the establishment of integrated wound care centers have impacted the care of patients with CLTI and, therefore, may have also assisted to decrease the overall rate of amputation.[41,50]

Trends in Amputation Risk Among Those With PAD and Diabetes Mellitus Over Time

Despite the overall decline in amputation rates described above, the trends in amputation among those with concomitant PAD and diabetes mellitus differ. A study within the state of California found amputation rates in this cohort had declined between 2005 and 2008 but had plateaued and remained stable through 2011 at ≈31 per 1 million Californians.[51] An additional study from the same group focused on those with ulceration found amputation rates increased nearly 3-fold between 2005 and 2013, from 10% to nearly 30%, among patients in California with diabetes mellitus and CLTI.[44] These data demonstrate that risks for patients with diabetes mellitus and PAD remain a significant priority in amputation prevention, even as results have improved for other patient subgroups.

Disparities in Amputation Risk

Within the United States, disparities in race, ethnicity, and geography exist such that amputation rates can be up to 9× higher—1800 per 100 000 Medicare patients—among

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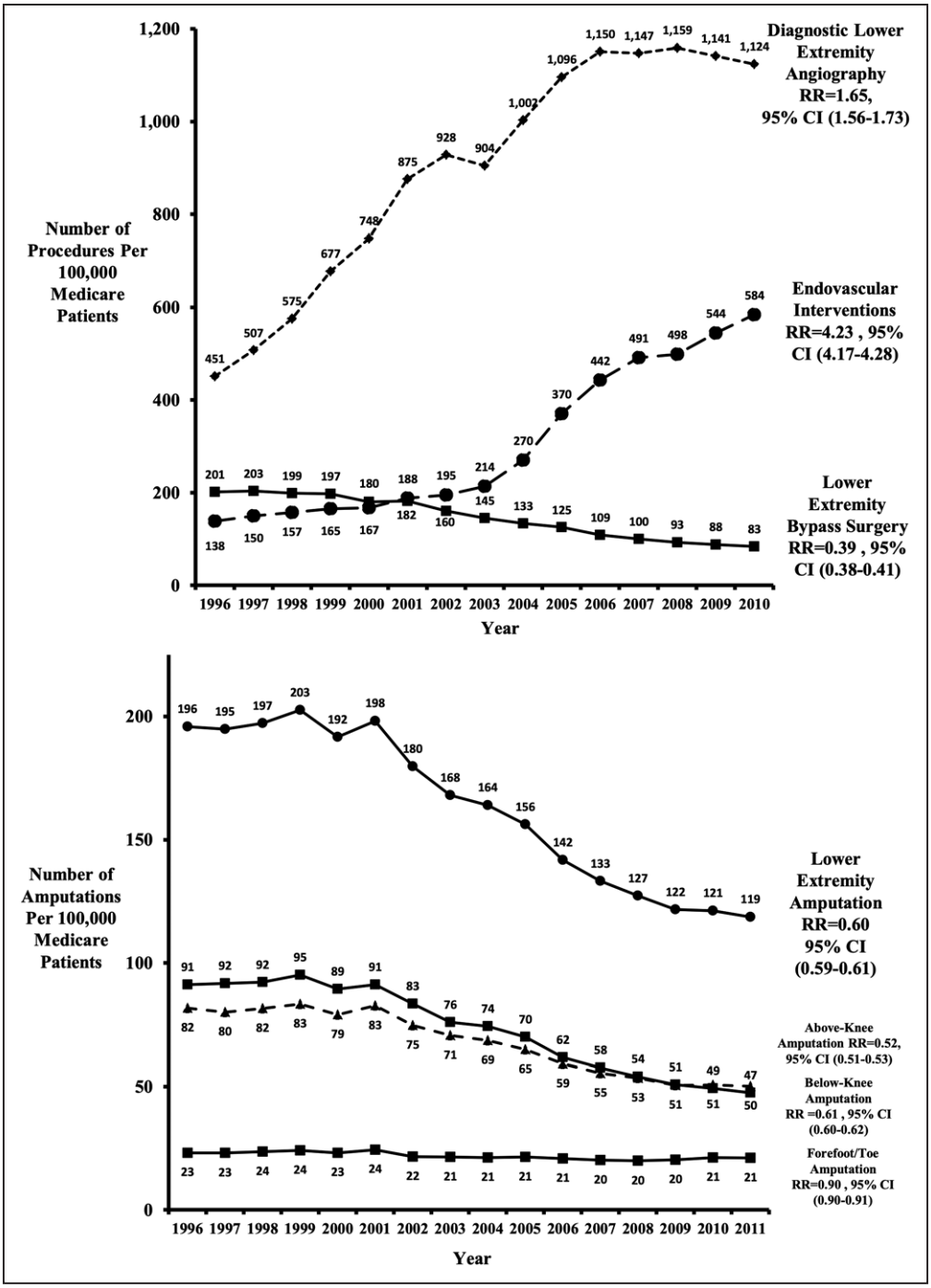

Figure 2. Trends in endovascular interventions, major amputation, and lower extremity bypass surgery 1996–2011.
RR, Risk ratio.[49]

African-Americans with diabetes mellitus in certain rural regions compared with non-African-Americans in more urban regions.[3,41] Henry et al[5] demonstrated an increased odds of amputation among African-American (odds ratio [OR], 2.9; $P<0.0001$) and Native American (OR, 2.4; $P<0.0001$) patients with PAD compared with white patients with PAD. Similarly, Goldberg et al[40] demonstrated that African-American patients with diabetes mellitus have an increased risk of amputation when compared with white patients with diabetes mellitus across risk strata. Within this study, 25.1% of the amputee cohort was African-American compared with 12.6% of the non-amputee cohort. Furthermore, Rizzo et al[52] demonstrated Native American patients with PAD were twice as likely to undergo amputation than non-Hispanic white patients with PAD.

Evaluation of revascularization attempts before amputation demonstrated that African-American patients

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were significantly less likely to undergo revascularization (Figure 3) when compared with white patients who had undergone amputation (OR, 0.72).[53] This same work similarly showed African-American patients who had undergone amputation were less likely to have been admitted or undergone wound debridement compared with white patients. The timing of revascularization in relation to amputation was similar across races/ethnicities and across varying durations of time, thus suggesting that late presentation could not explain the differences in care.[53]

In terms of socioeconomic status, PAD patients with lower socioeconomic status and Medicaid insurance coverage are more likely to undergo amputation.[5,54] Specifically, those in the lowest income quartile were at 34% higher odds of undergoing an amputation when compared with those in the highest income quartile (OR, 1.34; $P<0.0001$).[5] Similarly, Medicaid coverage status placed patients at higher odds of amputation when compared to those with Medicare coverage (OR, 1.26; $P<0.0001$).

Broad variation has also been demonstrated at the international level where mean incidence rates of major amputations across different European and Australasian nations varied nearly 6-fold.[55] Within this analysis, factors such as the prevalence of diabetes mellitus or smoking, population age, and healthcare reimbursement models, such as fee-for-service versus population-based reimbursement, were compared. Although each varied, only healthcare reimbursement models yielded a significant difference in amputation rates. Major amputations were less common in fee-for-service nations compared to nations with population-based reimbursement models. Similarly, amputations were more common in countries with lower national gross domestic product per capita and healthcare expenditures as a percent of gross domestic product.

BURDEN AND COST OF AMPUTATION

Amputation related to diabetes mellitus and PAD presents a tremendous burden on patients, families, and society. At the patient level, of those who undergo amputation as a result of diabetes mellitus or PAD, >55% are permanently disabled thereafter. A similar number, especially those who undergo above-knee amputation, never return to an ambulatory status.[56] Among patients who had undergone major amputation for CLTI (amputation either below or above the knee), 1-year mortality was 40.4% in a recent US Medicare study; this was 10% higher, in absolute terms, when compared with patients diagnosed with CLTI who did not undergo amputation, where the 1-year mortality rate was 30%.[32,57] These rates manifest the severity of this disease over time, as the 5-year mortality associated with CLTI without amputation is estimated to be 55% to 65%.[32] As shown in Table 1, this exceeds the 5-year mortality of female breast cancer (10%), colon cancer (35%), and myeloma (50%).[58]

Estimates of Financial Impact of Amputation

Within health systems, patients with concomitant diabetes mellitus and PAD pose a significant strain on the United States' healthcare system. Total annual Medicare expenditures on these patients with PAD are estimated to exceed

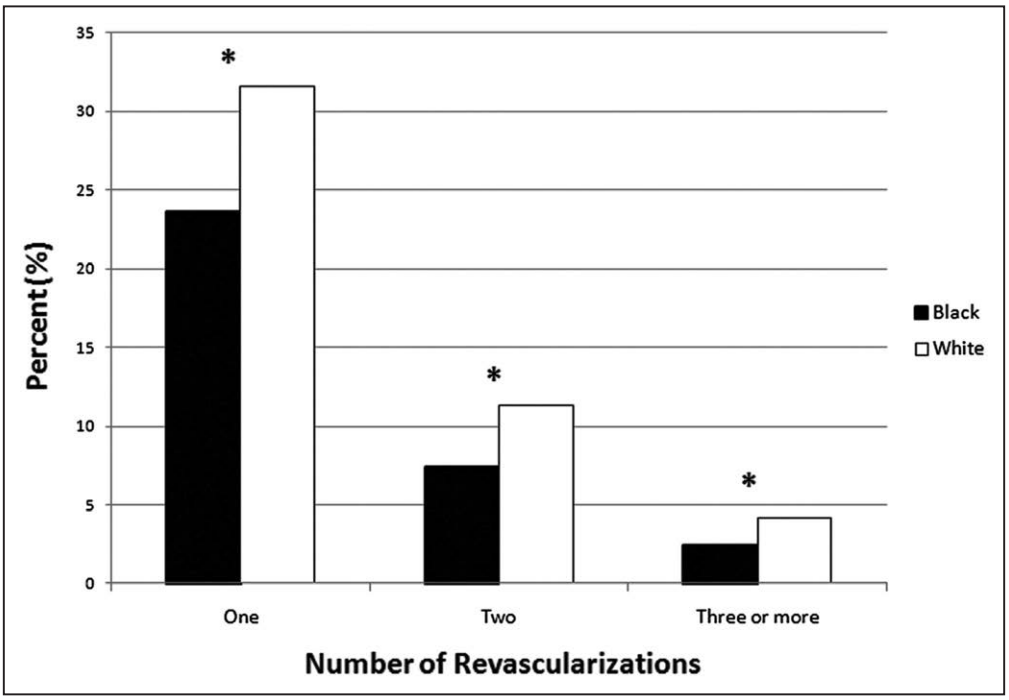

Figure 3. Percentage of patients undergoing revascularization before amputation.
*$P<0.0001$. Reprinted from Holman et al[53] with permission. Copyright ©2011, Elsevier.

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Table 1. Comparison of 5-Year Mortality Rates Across Disease Processes

Disease	5-Year Mortality Rate
CLTI without amputation	55%–65%[32]
Female breast cancer	10%[58]
Bladder cancer	23%[58]
Colon cancer	35%[58]
Myeloma	50%[58]
Lung and bronchus cancer	82%[58]
Pancreatic cancer	92%[58]

CLTI indicates chronic limb-threatening ischemia.

$84 billion per year, with some estimates ranging to as high as $381 billion per year if costs associated with long term care are included.[57,59,60] Among individuals with PAD who require intervention, those who also have diabetes mellitus are the costliest with an average annual Medicare spending of ≈$120 000 per patient compared with $70 000 in those without diabetes mellitus per treatment year.[59]

ADDRESSING AMPUTATION RISK IN PATIENTS WITH DIABETES MELLITUS AND PAD

For patients with diabetes mellitus and PAD, preventative care and care coordination are critical in avoiding progression to CLTI, ulceration, and eventually amputation. Integrated management strategies for diabetes mellitus and CLTI, defined as hemoglobin A1c testing, diabetic foot care, and vascular assessment, have been shown to help limit amputation in patients with diabetes mellitus and CLTI.[61–63] Furthermore, each of these tests or examinations are routine, frequently ordered, and inexpensive.[61] These integrated management strategies have been put forward by the American Heart Association, the National Committee on Quality Assurance, the American Diabetes Association, and the Society for Vascular Surgery, among others, in the form of practice guidelines outlining evidence-based benchmarks of care for patients with PAD and recommendations for risk factor modification (Table 2).[64–67]

Despite these recommendations, implementation of these guidelines in practice varies. As it pertains to hemoglobin A1c testing, specifically, a report from The Dartmouth Atlas in 2014 demonstrated this variation in utilization using Medicare claims data (Figure 4).[75] Hemoglobin A1c testing was utilized relatively less frequently in the Southern and Western regions of the United States (Albuquerque, NM 66.9%, Anchorage, AK 69.8%, Lawton, OK 73.8% percent of diabetic Medicare beneficiaries received testing) when compared with the upper Midwest (Rochester, MN 92.7%, Marshfield, WI 92.3%).[75] There was also significant variation in the care provided when stratified by ethnicity. African-American patients were less likely to receive the recommended preventative measures. Specifically, 84.2% of non-African-American patients received hemoglobin A1C testing, whereas only 80.9% of African-American patients underwent this testing.

CONCLUSIONS

Overall, the concomitant existence of PAD and diabetes mellitus lends significant complexity to the management of these conditions. Patients with both conditions face significantly higher risks of amputation than patients with either disease process in isolation. These conditions, especially in certain populations of patients, impart several-fold higher risks of amputation and poor survival, and these risks are greatest in many of the United States' most vulnerable populations. Furthermore, although complex and expensive treatments such as endovascular interventions are often necessary, research suggests that simple, inexpensive, and evidence-based measures, such as hemoglobin A1c testing, diabetic foot care, and vascular assessments, are underused.

The pathway ahead for those who care for patients with PAD and diabetes mellitus will require a better understanding of which groups within these high-risk

Table 2. Integrated Management Strategies to Limit Amputation for Patients With Diabetes Mellitus and CLTI

		Integrated Management for Diabetes Mellitus and CLTI		
Organization	Program/Document	HgA1c Testing	Diabetic Foot Care	Vascular Assessment
HRSA[68,69]	LEAP	HgA1c, patient education	Annually	Physical exam and ABI
AHA/APMA/SVS[67]	Strategies to prevent and heal diabetic foot ulcers	HgA1c, patient education	Annually	Physical exam and ABI
VAMC[70–72]	STAMP	HgA1c, patient education	Annually	Physical exam and ABI
Healthy People 2020[73]	Diabetic objective D-4	HgA1c, patient education	Annually	Physical exam and ABI
ADA[65]	Position statement on preventive foot care	HgA1c, patient education	Annually	Physical exam and ABI
International Diabetes Federation[74]	Position statement on preventive foot care	HgA1c, patient education	Annually	Physical exam and ABI

ABI indicates Ankle-Brachial index; ADA, American Diabetes Association; AHA, American Heart Association; APMA, American Podiatric Medical Association; CLTI, chronic limb-threatening ischemia; HgA1c, hemoglobin A1c; HRSA, Health Resources & Services Administration; LEAP, Lower Extremity Amputation Prevention Program; STAMP, Special Teams for Amputation, Mobility, and Prosthetics; SVS, Society for Vascular Surgery; and VAMC, Veterans Affairs Medical Centers.

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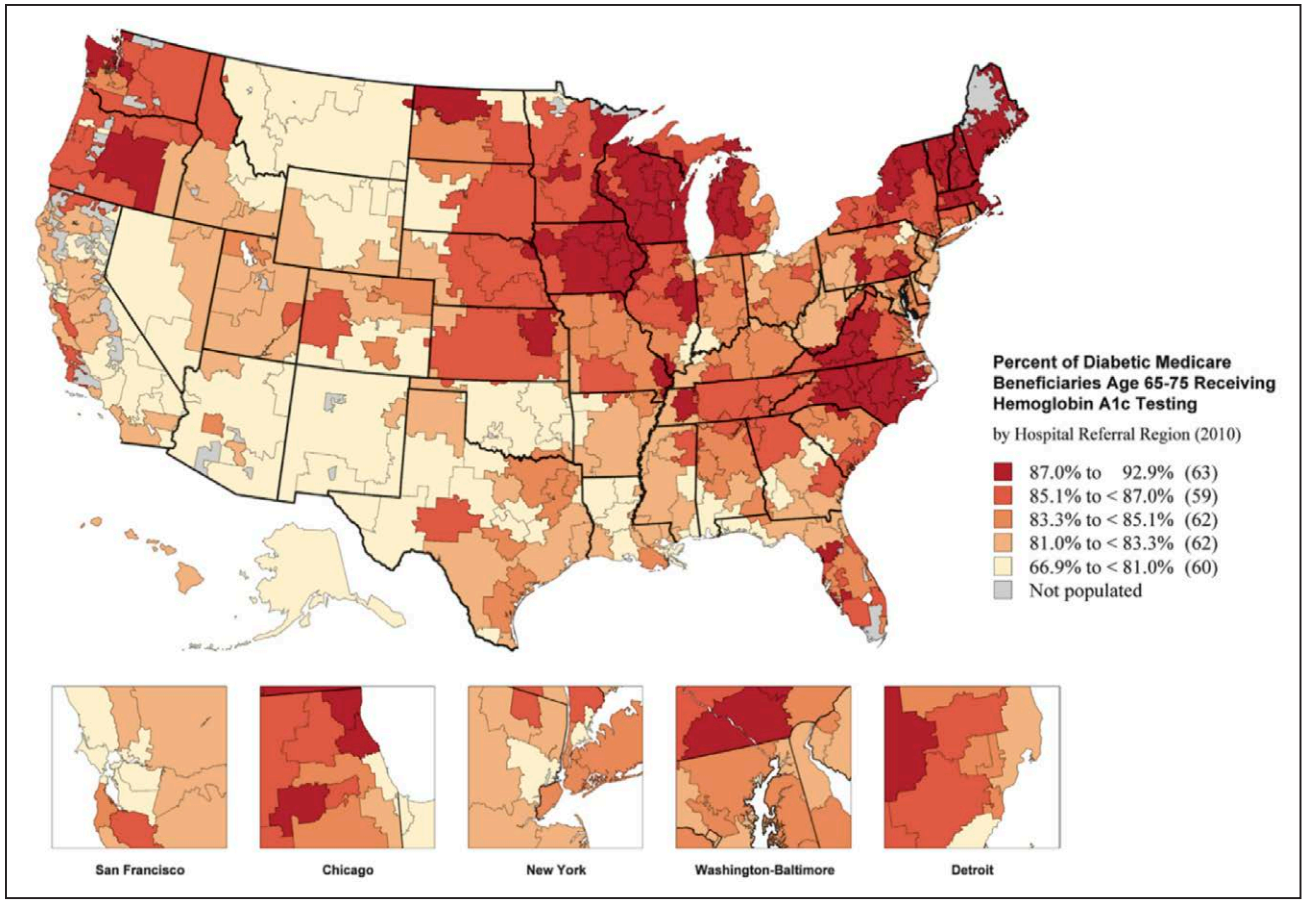

Figure 4. Percent of diabetic Medicare beneficiaries receiving hemoglobin A1c testing (2010).
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subgroups—Native Americans, African-Americans, the rural poor—are subject to the highest risks of amputation. A clearer vision of the epidemiology, pathophysiology, and health care delivery present in these populations, as well as the social, economic, and structural barriers which are implicit in their excess risks of limb loss, is urgently needed. Although these tasks present obvious challenges, it is important that in further limiting amputation risk, we study the patients at the greatest risk where amputation rates remain unacceptably high. The challenges ahead will be multidisciplinary and complex, but successful reduction of amputation risk among patients with PAD and diabetes mellitus is too important of a goal to fade from these challenges.

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