Limb- and Person-Level Risk Factors for Lower-Limb Amputation in the Prospective Seattle Diabetic Foot Study

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OBJECTIVE

Diabetes is the leading cause of nontraumatic lower-limb amputations in the U.S., but no research has prospectively examined associations between limb-specific measurements and amputation risk among patients without foot ulcer. We investigated amputation risk by limb in relation to the same limb- and person-level factors.

RESEARCH DESIGN AND METHODS

We conducted a 22-year prospective study among 1,461 male patients with diabetes without foot ulcer (mean age 62.4 years), with 2,893 lower limbs among subjects recruited between 1990 and 2002 from one veterans affairs General Internal Medicine Clinic. The following information was collected: demographic, lifestyle, and diabetes characteristics; visual acuity; kidney function (estimated glomerular filtration rate [eGFR]); and lower-limb measurements including presence of Charcot deformity, sensory neuropathy by 10-g monofilament, dorsal foot transcutaneous oximetry ($TcPO_2$) at 44°C, and ankle-brachial index (ABI).

RESULTS

Over 25,735 limb-years, 136 amputations occurred. A multivariable Cox model identified multiple independent risk factors: sensory neuropathy (hazard ratio 3.09 [95% CI 2.02–4.74]), ABI ≤0.5 vs. >0.9 to <1.3 (3.98 [2.31–6.85]), ABI ≥1.3 vs. >0.9 to <1.3 (2.20 [1.18–4.09]), 1-SD decrease in eGFR (1.18 [1.00–1.38]), poor vision (1.70 [1.05–2.73]), body weight in 21.4-kg increments (0.78 [0.61–0.98]), and age >70 years vs. <57 years (0.13 [0.04–0.38]). Although $TcPO_2$ was not significantly associated with amputation overall, $TcPO_2$ <26 mmHg significantly predicted a higher risk in the ABI ≥1.3 category.

CONCLUSIONS

Arterial disease and neuropathy emerged as the only limb-specific risk factors for amputation, but these and several person-level factors may be amenable to prevention or treatment interventions to potentially reduce diabetic amputation risk.

Diabetes increases risk of lower-limb amputation, but this outcome has received less attention than the eye, renal, and cardiovascular complications of this metabolic disorder. In the U.S., more than half of nontraumatic amputations are attributable to diabetes (1). Despite the major role diabetes plays in limb loss, research on limb-specific factors that predict this outcome in patients without foot ulcer is, to the best of our knowledge, nonexistent. The lack of such research is probably due to the

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infrequency of this event. A recent study of 26 Organization for Economic Development and Cooperation countries found a median rate of 7.8 events/100,000 persons with diabetes (2). A review of global variation in incidence that mainly included European countries and the U.S. found annual incidence ranging from 4.6 to 960/10,000 persons, but 85% of countries/states examined had an annual incidence <100/10,000 (3). The low incidence of diabetic amputation requires that research on risk factors for this complication have a large sample size and prolonged follow-up to enable testing of hypotheses regarding predictors of limb loss with adequate statistical power. Therefore, much of the research on the epidemiology of diabetic amputation is based on health plan medical record data, large surveys, or regional or national hospitalization data, since amputation is a procedure performed on inpatients only, thereby generating a hospital discharge summary and diagnosis codes (4–8). Research based on such data are limited to person-level factors that are commonly measured in the process of clinical care, such as demographics, clinical laboratory measurements, presence of comorbid conditions, and other characteristics. The shortcomings of such research are obvious when one considers that the major risk factors for diabetic foot ulcer, the important precursor to amputation, are limb-specific measurements of neuropathy, arterial perfusion, foot deformity, and foot pressure (9–12).

To address the need for a comprehensive assessment of limb-specific and person-level risk factors for diabetic foot complications including foot ulcer and amputation, we launched a large prospective study in 1990 with an initial follow-up over 12 years. Using electronic medical record data, we have extended this follow-up to a maximum of 22 years. This article reports our findings regarding the independent predictors at both the limb and person levels of diabetic lower-limb amputation.

RESEARCH DESIGN AND METHODS

Study Subjects

All ambulatory general internal medicine clinic patients at VA Puget Sound Health Care System - Seattle Division with diabetes were eligible for enrollment. Recruitment of study participants commenced in 1991 and continued through 2001. Written informed consent was obtained from all study participants. Exclusion criteria included current foot ulcer, bilateral foot amputations, being wheelchair bound or unable to walk, being too sick to participate, and psychiatric illness that prevented informed consent. Subjects with clinically apparent diabetes were identified by review of hospital computerized pharmacy data for receipt of insulin, oral hypoglycemic medication, or blood or urine glucose test strips; review of laboratory data; and review of medical record problem lists for the diagnosis of diabetes. The diagnosis was then confirmed by communication with clinical providers or medical record review.

IRB Approval

The University of Washington Human Subjects Office and the VA Puget Sound institutional review board approved this research.

Clinical Interview and Physical Exam Measurements

Subjects were interviewed for collection of data on demographics; diabetes type, duration, and treatment; smoking history; foot-related self-care behaviors; neuropathic symptoms; and history of foot or leg ulcer and amputation. A physical exam with emphasis on the lower limbs was performed by research nurse practitioners, who assessed presence of Charcot deformity by clinical assessment. Visual acuity was assessed with a Snellen chart and defined as poor if 20/70 or worse in both eyes. Weight in kilograms was measured with a balance beam scale.

Laboratory and Neurovascular Measurements

Sensory testing was performed at nine locations on each foot using the Semmes-Weinstein monofilament (13). Inability to perceive the 5.07 monofilament at one or more sites on a foot was considered to represent peripheral sensory neuropathy in that foot. Measurements of lower-limb transcutaneous O_2 tension ($TcPO_2$) were performed at 44°C with TCM-3 monitors (Radiometer, Copenhagen) under uniform conditions on the dorsal foot just proximal to the second toe and the plantar hallux (14). Brachial and lower-limb arterial blood pressures in both limbs over the posterior tibialis and dorsalis pedis arteries were measured by standard Doppler techniques (MedaSonics, Fremont, CA) (15). The ankle-brachial index (ABI) was calculated as the ratio of the ankle systolic pressure (defined as the higher of the dorsalis pedis or posterior tibialis measurements) divided by the higher brachial systolic pressure. A random blood sample was drawn for measurement of glycosylated hemoglobin (Isolab, Akron, OH), serum creatinine (Hitachi 917 autoanalyzer; Boehringer Mannheim, Indianapolis, IN), and serum albumin (Hitachi 917 autoanalyzer; Boehringer Mannheim). Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on serum creatinine, age, sex, and race (16).

Outcome Assessment

Occurrence of lower-limb amputation was recorded during research clinic follow-up appointments and medical record review from 1990 to 2002. Amputation occurrence was also captured from review of electronic health records, specifically, national Department of Veterans Affairs (VA) and Centers for Medicare and Medicaid Services (CMS). National inpatient and western region (nine states including AK, WA, OR, ID, NV, CA, AZ, NM, and HI) outpatient hospitalization records from 1 January 1990 to 31 December 2012 were queried for the presence of lower-extremity amputation procedure codes (84.1x). For those people who were identified as having a lower-limb amputation, we examined the complete medical records for an indication of which limb was removed, as ICD-9 codes do not include laterality. When multiple amputations occurred on the same limb within 30 days, or within the same hospitalization, the amputation date was set to the first date, and the amputation level was set to the highest level. Date of death was determined using VA vital status file (17).

Statistical Analysis

Frequencies of categorical characteristics and means of continuous measurements were calculated. The following analyses were conducted with each limb as the subject. Kaplan-Meier Curves were plotted to display time to amputation by categorical characteristics of interest. Cox proportional hazards models were fit to identify independent predictors of amputation, while accounting for within-subject correlation between each limb. Univariate models were fit that included the baseline measurement only. Fully adjusted models included all exposure variables and allowed measurements to vary

over time when updated on repeated examinations. Updated measurements included those shown in Table 1 except for sex and foot ulcer or amputation prior to study enrollment. The final adjusted models were determined using stepwise reduction, maintaining all exposure variables with $P < 0.10$. Interactions were assessed by the insertion of first-order interaction terms in Cox models containing both main effects. $P < 0.05$ was considered statistically significant. All analyses were performed with Stata 13 (College Station, TX). The proportional hazards assumption of our multivariable model was tested using the Stata command estat phtest and found to be valid. Statistical models were fit using the Stata cluster and robust variance options to account for the correlation between limbs in a given patient.

Table 1—Limb-level and person-level baseline population characteristics by lower-limb amputation status among 1,487 veterans with diabetes (1990–2012)

	Total population (*N* feet)[a]	Percent with amputation	Males only (*N* feet)	Percent with amputation
Sample	2,945	4.7	2,893	4.7
Person-level measurements				
Sex				
Male	2,893	4.7		
Female	52	1.9		
Age, years				
≤56	855	4.7	841	4.5
57–64	679	7.5	667	7.5
65–70	729	5.8	717	5.9
>70	682	0.9	668	0.9
Foot ulcer prior to enrollment				
No	2,372	3.4	2,326	3.3
Yes	559	10.6	553	10.7
Amputation prior to enrollment				
No	2,844	4.3	2,792	4.2
Yes	101	18.8	101	18.8
Insulin use				
No	1,747	2.9	1,709	2.9
Yes	1,193	7.1	1,179	7.2
Lifetime smoking history				
No	548	4.7	520	4.8
Yes	2,395	4.6	2,371	4.7
Visual acuity				
Normal to near normal (<20/70)	2,378	4.5	2,336	4.6
Poor vision (20/70–20/200)	529	5.5	519	5.4
eGFR (categorical), mL/min/1.73 m^2				
<15	14	21.4	14	21.4
15–29	73	10.9	73	10.9
30–59	837	4.4	807	4.5
60+	1,991	4.5	1,969	4.5
Limb-level measurements				
Neuropathy				
No	1,831	2.7	1,785	2.7
Yes	1,089	8.0	1,083	8.0
Charcot deformity				
No	2,911	4.5	2,859	4.5
Yes	29	24.1	29	24.1
Dorsal foot $TcPO_2$, mmHg				
<26	289	4.2	285	4.2
26–45	984	4.8	974	4.8
46+	1,356	5.2	1,324	5.2
ABI				
≤0.5	139	7.2	138	7.3
0.5 < ABI ≤ 0.9	618	6.9	612	6.9
0.9 <ABI <1.3	1,776	3.7	1,739	3.7
≥1.3	202	5.4	196	5.6

[a]Includes 26 women who were excluded from further analyses owing to their small number.

Results

A total of 1,487 participants were enrolled without foot ulcer. Of these, 26 were women whom we excluded from these analyses owing to their small number. The remaining 1,461 men contributed 2,893 limbs, and the total follow-up time in limb-years was 25,735. During follow-up, 136 amputations occurred (65% above the ankle) and 869 participants died. The amputation incidence was 5.3/1,000 limb-years. Participants underwent between 1 and 8 examinations during follow-up, with the average number of evaluations equal to 3.5. The occurrence of foot ulcer prior to amputation could only be accurately determined during the time period when participants were followed in a research clinic (1990–2002) and not afterward when electronic health record data were used to capture amputation outcomes. Between 1990 and 2002, 50 amputations occurred, of which 39 (79%) were preceded by a foot ulcer.

Baseline mean values for participants were age 62.4 years, diabetes duration 15.1 years, HbA_{1c} 9.6% (81 mmol/mol), systolic blood pressure 141 mmHg, weight 97.7 kg, serum albumin 43.4 g/L, and eGFR 75 mL/min/1.73 m^2. Baseline mean values for limbs were ABI 1.0 and $TcPO_2$ 46.0 mmHg. Characteristics of limbs and cumulative risk of lower-limb amputation are shown in Table 1. A higher risk of amputation was seen with the middle age categories, prior amputation or foot ulcer, insulin use, poor vision, neuropathy, Charcot deformity, low and high ABI, and lower eGFR and $TcPO_2$.

Hazard ratios for participant characteristics for unadjusted and adjusted models that include the baseline measurement only and adjusted models that included time-varying measurements are shown in Table 2. In unadjusted analyses, baseline measurements of the following characteristics were significantly associated with amputation risk: age, prior foot ulcer or amputation, insulin use, poor vision, HbA_{1c}, eGFR, serum albumin, systolic blood pressure, neuropathy, Charcot deformity, and ABI. We fit a Cox proportional hazards model that included all the variables shown in Table 2. As

Table 2—Unadjusted and adjusted hazard ratios for lower-limb amputation among male veterans with diabetes (1990–2012)

	HR (95% CI), unadjusted; *N* feet = 2,893	HR (95% CI), adjusted; *N* feet = 2,408
Person-level measurements		
Age, years		
≤56	1.00	1.00
57–64	**2.05 (1.25, 3.36)**	1.21 (0.69, 2.14)
65–70	**1.85 (1.11, 3.09)**	0.94 (0.52, 1.72)
Over 70	**0.34 (0.14, 0.81)**	**0.13 (0.04, 0.38)**
Foot ulcer prior to enrollment		
No	1.00	1.00
Yes	**3.49 (2.33, 5.23)**	1.54 (0.97, 2.45)
Amputation prior to enrollment		
No	1.00	1.00
Yes	**6.68 (3.76, 11.88)**	2.13 (0.95, 4.80)
Insulin use		
No	1.00	1.00
Yes	**2.87 (1.87, 4.40)**	1.42 (0.87, 2.32)
Lifetime smoking history		
No	1.00	1.00
Yes	1.16 (0.67, 2.00)	0.71 (0.42, 1.21)
Visual acuity		
Normal to near normal (<20/70)	1.00	1.00
Poor vision (20/70–20/200)	**2.78 (1.85, 4.16)**	**1.70 (1.05, 2.73)**
Weight[a]	0.87 (0.71, 1.07)	**0.78 (0.61, 0.98)**
Diabetes duration[a]	1.12 (0.97, 1.30)	1.09 (0.89, 1.33)
HbA_{1c}	**1.10 (1.04, 1.17)**	1.04 (0.96, 1.13)
eGFR (continuous)[b]	**1.46 (1.33, 1.59)**	**1.18 (1.00, 1.38)**
Serum albumin[a]	**0.62 (0.52, 0.75)**	0.84 (0.68, 1.03)
Systolic blood pressure[a]	**1.56 (1.28, 1.90)**	1.24 (0.99, 1.55)
Limb-level measurements		
Dorsal foot $TcPO_2$ at 44°C[a]	0.90 (0.70, 1.15)	0.97 (0.79, 1.20)
Neuropathy		
No	1.00	1.00
Yes	**4.81 (3.18, 7.26)**	**3.09 (2.02, 4.74)**
Charcot deformity		
No	1.00	1.00
Yes	**3.51 (1.18, 10.42)**	2.14 (0.76, 6.02)
ABI		
≤0.5	**6.23 (3.81, 10.18)**	**3.98 (2.31, 6.85)**
0.5 < ABI ≤ 0.9	**2.39 (1.50, 3.81)**	**1.88 (1.13, 3.11)**
0.9 <ABI <1.3	1.00	1.00
≥1.3	**2.53 (1.34, 4.78)**	**2.20 (1.18, 4.09)**

Statistically significant results appear in boldface type ($P < 0.05$). [a]Hazard ratios for these variables are for a 1-SD increment. For weight, this is 21.4 kg, for diabetes duration this is 12 years, for $TcPO_2$ this is 16 mmHg, for albumin this is 3.6 g/L, and for systolic blood pressure this is 22 mmHg. [b]eGFR was transformed for these analyses to 1/(eGFR/100).

participants had multiple measurements of exposures of interest during follow-up, we included these time-varying exposure measurements as well as the few non–time-varying exposures (amputation or foot ulcer prior to enrollment). Both age >70 years and greater weight were associated with a reduction in risk of amputation, while a higher risk of amputation was seen with poor vision, neuropathy, low eGFR, and both low and high ABI (Table 2). Interactions between neuropathy and both $TcPO_2$ and ABI were tested and found to be not significant ($P = 0.299$ and $P = 0.307$).

We examined further the associations between the vascular measurements that we performed and amputation risk. Kaplan-Meier curves of amputation-free survival by ABI are plotted in Fig. 1. The highest amputation risk is seen with a severely low ABI ≤0.5 and the lowest amputation risk in the ABI category generally considered to indicate no peripheral arterial disease (0.9 < ABI < 1.3). Intermediate amputation risk was seen not only in the moderately low ABI category of >0.5 and ≤0.9 but also with ABI ≥1.3. The amputation risk appeared equivalent for ABI between >0.5 to ≤0.9 and ≥1.3. The Kaplan-Meier curves are not adjusted for covariates. The adjusted model in Table 2 also confirms a similar pattern of associations, with the higher amputation risk seen in participants with ABI ≤0.5 and a lesser elevation of risk with ABI between >0.5 to ≤0.9 and ≥1.3.

No significant association was seen between $TcPO_2$ and amputation risk in the Cox unadjusted and adjusted models (Table 2). Amputation-free Kaplan-Meier survival curves by $TcPO_2$ categories were plotted (Fig. 2). Although the lowest $TcPO_2$ category appeared to diverge from the other two categories after ~4,000 days of follow-up, indicating lower amputation-free survival, this difference was not statistically significant (Fig. 2*A*). We further examined whether $TcPO_2$ might provide better discrimination of amputation risk by ABI category. We found that $TcPO_2$ <26 mmHg in the ABI ≥1.3 category significantly predicted a higher risk for amputation development (Fig. 2*B*). No associations were seen between amputation-free survival and $TcPO_2$ categories in the other ABI categories (data not shown).

CONCLUSIONS

These results support a complex etiology for diabetic amputation that includes person- and limb-level factors. The two limb-level factors that emerged as independently associated with amputation risk in the analysis that incorporated time-varying measurements of exposure reflected function of the circulatory and nervous systems. Macrovascular disease as measured by the ABI demonstrated a U-shaped association with amputation risk, as both lower and higher levels were associated with greater amputation risk. An ABI of ≤0.5 was associated with the greatest elevation of risk among all factors that we considered in multivariable analysis, suggesting that poor perfusion plays perhaps the most important role in the pathway to amputation. Interestingly, an elevated ABI ≥1.3, was also associated with a greater than twofold increase in amputation risk. A high ABI is thought to reflect medial arterial disease, which is found more frequently in diabetes, and this condition may cause luminal stenosis and impaired perfusion (18). Incompressible vessels, however, may not reflect luminal stenosis. To investigate this further, we used another measure of perfusion that is not dependent on

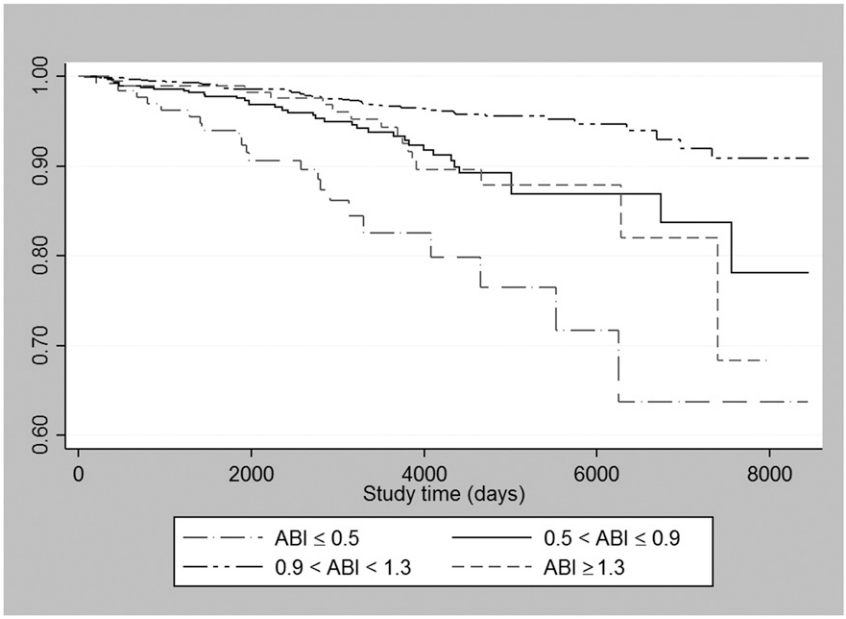

Figure 1—Kaplan-Meier curves of amputation-free survival by ABI categories.

arterial vessel compression for its measurement, namely, $TcPO_2$. We previously demonstrated a low correlation between $TcPO_2$ and lower-limb perfusion measurements (19). We found that this measurement further differentiated participants with high ABI into distinct risk categories based on $TcPO_2$ values. Although $TcPO_2$ overall and in participants with ABI $<$1.3 did not help to distinguish risk differences among all subjects, it appears to provide additional potentially valuable information on amputation risk in persons with arterial stiffness and incompressible vessels.

Neuropathy as captured by 10-g monofilament testing also predicted higher amputation risk, likely due a cascade of events beginning with foot injury/ulceration owing to loss of protective sensation and subsequent infection necessitating amputation (20). The hazard ratio associated with neuropathy was of the second-highest magnitude in both unadjusted and adjusted Cox proportional hazards analysis. In addition, sensory neuropathy was a very common finding in this population, with 37% of participants testing positive for this characteristic at baseline. The vast majority of diabetic lower-limb amputations are preceded by a foot ulcer, as was also seen in this study during the time period when patients were being monitored for ulcer occurrence, and arguably the most important risk factor in the development of this skin defect is the presence of sensory neuropathy (11,20–22).

Person-level factors independently associated with amputation risk included age, weight, visual acuity, and renal function. Diminished renal function was independently associated with greater amputation risk, and this same association has been reported with risk of cardiovascular disease (23). Renal impairment may be causally related to the development of amputation in addition to serving as a marker for disease burden. Poor vision was also independently associated with higher amputation risk, and may also serve as a marker for disease burden, but may also impair foot self-care and lead to diminished ability to identify and treat lower-extremity lesions that might set the stage for amputation.

Several surprising and counterintuitive person-level findings also emerged from this analysis. It is not clear why a lower risk of amputation was seen in participants age $\geq$70 years. Our adjustment for diabetes duration removed the possible explanation that this might be due to the development of diabetes later in life, with fewer remaining years in which to develop foot and other diabetes complications. Another possible explanation is an age-cohort effect, but it is unclear why membership in an earlier generation would confer better limb outcomes. We considered the possibility that the lower risk of amputation in older ages might be due to death as a competing risk and performed a competing risks regression analysis of age as a predictor of amputation, but the results of this analysis yielded hazard ratios nearly identical to those in the unadjusted results shown in Table 2 (data not shown). A similarly counterintuitive finding was seen with the association between body weight and diabetes risk, with a lower amputation risk seen with greater body weight. Given the likely role of body weight in leading to greater plantar pressure, a cause of diabetic foot ulcer, one would have expected greater weight to be associated with greater amputation risk (24). Another possibility to explain this association is a variant of the "obesity paradox" that has been demonstrated in multiple diseases, including diabetes, with lower incidence of multiple health outcomes associated with greater body weight, including mortality and amputation, possibly due to reverse causation (25,26).

Several characteristics that significantly predicted amputation risk in univariate analysis became insignificant after adjustment but just barely so. In general, this may be explained by these characteristics not being independent of each other. These include prior history of foot ulcer and amputation, HbA_{1c}, insulin use, and systolic blood pressure. As high HbA_{1c} may lead to neuropathy and insulin use, and elevated systolic blood pressure to peripheral arterial disease, the decline in the strength of the association between these characteristics and amputation risk may potentially be explained by adjustment for mediating factors (27). History of foot ulcer and amputation likely serve as markers for neuropathy and vascular disease, and thus the decline in the magnitude of these associations with amputation risk may be due to control of confounding. Similarly, serum albumin may serve as a marker for inflammation and poor nutrition, and adjustment for factors related to either or both would have served to diminish its association with amputation risk (28). Charcot deformity also failed to show an independent association with amputation risk in adjusted analysis, possibly due to its association with neuropathy and perhaps because of the small number of participants affected by this condition leading to low statistical power (n = 29).

Our research has several strengths. To our knowledge, this is the first study to examine prospectively the risk of amputation in relation to limb-level measurements by

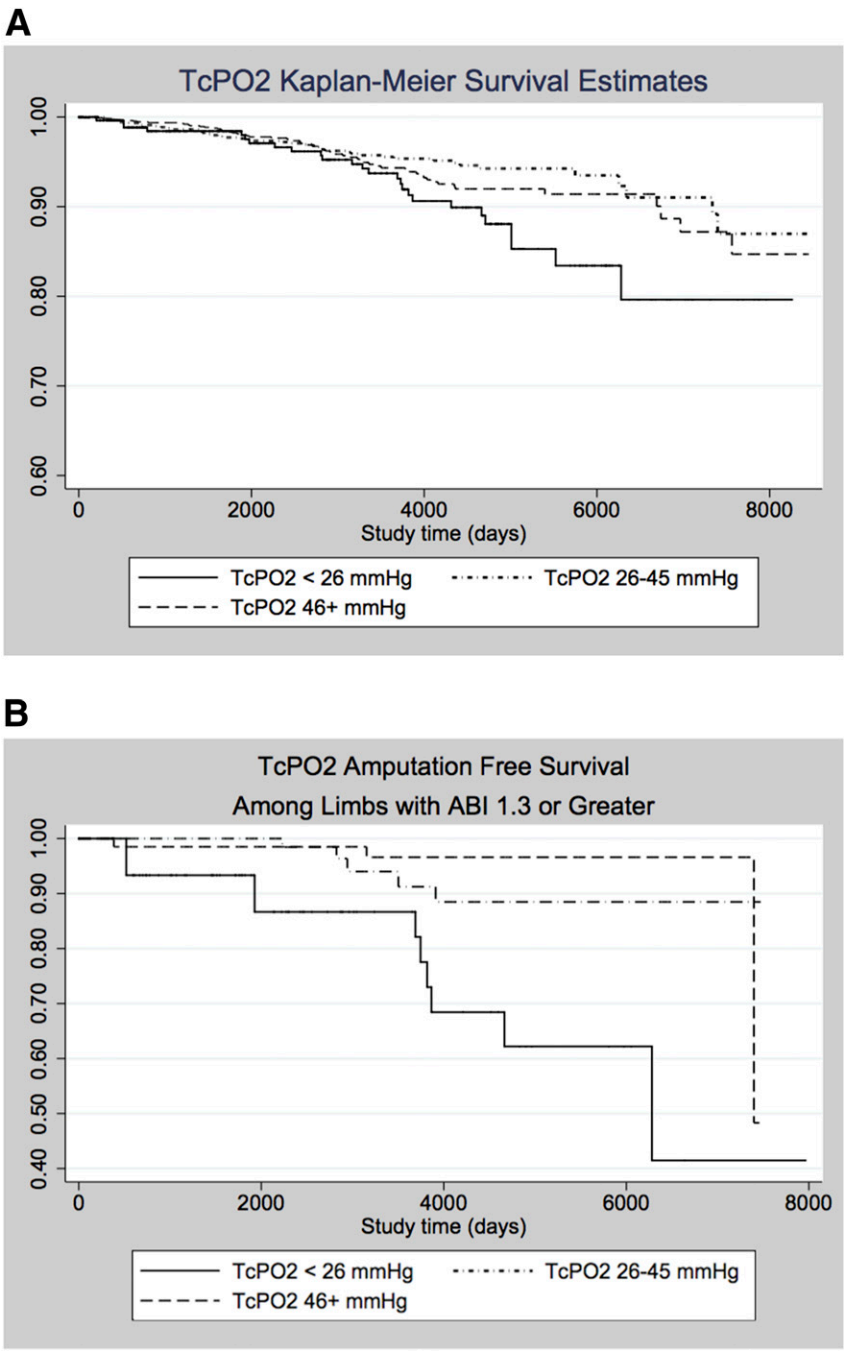

Figure 2—Kaplan-Meier curves of amputation-free survival by $TcPO_2$ categories. *A*: Among all participants. *B*: Among participants with ABI ≥1.3. (A high-quality color representation of this figure is available in the online issue.)

considering each limb as the unit of analysis. A previous analysis conducted in this same cohort after a median follow-up of 3.3 years and a total follow-up of 2,305 person-years, during which time only 30 lower-limb amputations had occurred, included a person-level analysis using only one lower limb–specific measurement (29). The current analysis took advantage of the >10-fold increase in available person-years of follow-up and advances in statistical methodology to perform the limb-specific analyses reported in this article. The Strong Heart Study also reported the association between baseline ABI and risk of diabetic lower-limb amputation over an 8-year follow-up in an American Indian population (30). This analysis, however, was not conducted by limb. The lowest ABI was used in a person-level analysis (31). Furthermore, important confounding factors were not measured at baseline, including past history of foot ulcer and assessment of sensory neuropathy (30). Other research included limb-specific measurements but did not perform analysis by limb. A large prospective Scottish study in 15,983 patients with diabetes performed monofilament testing and palpation of peripheral pulses in the lower limbs but did not conduct an analysis of the association between these limb-specific measurements and ipsilateral amputation risk (32). Absent foot pulses and impaired monofilament sensation were each associated with an approximately sixfold increased risk of amputation. Martins-Mendes et al. (33) found that a sum of the dorsalis pedis and posterior tibialis pulses on both feet <1 predicted higher risk of amputation, but this combined sum is not foot specific. Several investigations in patients with chronic kidney disease included limb measurements of neurovascular function, with most finding an association between lower-limb amputation and presence of peripheral arterial disease and neuropathy using retrospective or cross-sectional study designs (34–37). None of these investigations, though, examined associations between amputation and limb-specific measurements in the same limb (34–37). A systematic review and meta-analysis of risk factors for amputation among patients on dialysis identified 21 studies on this topic, but a minority of these were prospective, and none of the prospective studies specifically assessed diabetic amputation risk by limb measurements in the same limb (38). The duration of follow-up of our research of up to 22 years is also unique among studies of amputation. The fact that hospitalization records capture all amputations and the availability of electronic hospitalization data permitted capture of outcomes well beyond the termination of the data-collection phase of this research in 2002. Furthermore, we conducted a comprehensive assessment of exposures that included many diabetes characteristics, health status and behaviors, and lower-limb measurements of perfusion, neuropathy, and deformity.

Also, there are several limitations that potentially may have led to bias. After the end of the active study data collection in 2002, we relied on electronic hospitalization records from the two most likely sources of medical care for our participants, namely, the VA and CMS. The latter

provides health insurance benefits in the U.S. for persons age ≥65 years and those with certain disabilities and medical conditions (e.g., end-stage renal disease and Amyotrophic Lateral Sclerosis). It is possible that we missed amputations in persons <65 years of age who ceased obtaining medical care in the VA system. Given that 48% of our participants were age ≥65 years when they entered the study, and that 72% of participants were ≥65 years at the end of follow-up, we believe that we had the ability to capture the outcome in the vast majority of participants with electronic medical record data from both VA and CMS systems but acknowledge that some participants might have been missed if they had left VA health care prior to age 65 years. Other limitations include restriction to males as a result of the small number of women enrolled, and inclusion of users of only one VA primary care clinic that agreed to participate in this investigation, thereby resulting in potential bias and limiting generalizability. Whether the results of this research apply to women, to persons enrolled in clinics in other health care settings, to those without an established health care provider, or to those unwilling to participate in research is not known. It is also not known whether these results apply to persons of ethnic groups not included in our population or to persons who reside in countries other than the U.S.

We conclude that this research has identified several potentially preventable or correctable factors that may lead to strategies to reduce the risk of this diabetes-related complication. Both sensory neuropathy and abnormally high ABI were shown to occur less frequently with intensive glycemic control in the Diabetes Control and Complications Trial, demonstrating that these two risk factors for amputation can be prevented by an intervention in type 1 diabetes (39,40). Low ABI resulting from occlusive atherosclerosis may be preventable with control of atherosclerosis risk factors through lifestyle intervention and pharmaceutical treatments to achieve cholesterol level reduction. Also, methods exist to slow the progression of diabetic nephropathy through use of intensive glycemic control and blood pressure treatment in both types 1 and 2 diabetes trials (41–43). Diabetic amputation rates over time are available in only a few instances from developed countries with better access to medical care. Results from the U.S., Denmark, and to a lesser extent Germany reveal a decline in the diabetic amputation rate occurring since the early 2000s, possibly due to better access to preventive treatments such as intensive glycemic control, cholesterol-reducing medications, and lifestyle modification (6,44,45). In addition, our results suggest potential opportunities for secondary prevention. The potential for correction of vision in preventing amputation is an area deserving further investigation. $TcPO_2$ may provide additional information to assist with risk characterization in patients with a high ABI owing to incompressible vessels. Hopefully, better knowledge of these limb- and person-level factors will result in continuing improvement in limb preservation among patients with diabetes through the development of remediation strategies.

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