Lower-Extremity Amputation in Diabetes

The independent effects of peripheral vascular disease, sensory neuropathy, and foot ulcers

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OBJECTIVE — To identify risk factors for lower-extremity amputation (LEA) in individuals with diabetes and to estimate the incidence of LEA.

RESEARCH DESIGN AND METHODS — This is a prospective study of 776 U.S. veterans in a general medicine clinic in Seattle, Washington. The outcome was first LEA during follow-up. Potential risk factors evaluated in proportional hazards models included, among others, peripheral vascular disease (PVD), sensory neuropathy, former LEA, foot deformities and ulcers, diabetes duration and treatment, and hyperglycemia.

RESULTS — Associated with an increased risk for LEA were PVD defined as transcutaneous oxygen ≤50 mmHg (relative risk [RR] = 3.0, 95% CI 1.3–7.1), insensitivity to monofilament testing (RR = 2.9, odds ratio = 1.1–7.8), lower-extremity ulcers (RR = 2.5, CI 1.1–5.4), former LEA, and treatment with insulin when controlling for duration of diabetes and other factors in the model. PVD defined as absent or diminished lower-extremity pulses or an ankle arm index ≤0.8 was also associated with a significantly higher risk of LEA in separate models. Foot ulcers were associated with an increased ipsilateral risk of amputation. The age-adjusted incidence among men only for LEA standardized to the 1991 U.S. male diabetic population was 11.3/1,000 patient-years.

CONCLUSIONS — This prospective study shows that peripheral sensory neuropathy, PVD, foot ulcers (particularly if they appear on the same side as the eventual LEA), former amputation, and treatment with insulin are independent risk factors for LEA in patients with diabetes.

Diabetes Care 22:1029–1035, 1999

Researchers have convincingly demonstrated that diabetes increases the risk of lower-extremity amputation (LEA) (1), but the factors that predispose to LEA are not clear, nor is the role that lower-extremity neuropathy, peripheral vascular disease (PVD), and ulcers each play in the genesis of LEA. Few studies have assessed the potential interrelationships of these factors by simultaneously assessing their relationship to risk of LEA (2). A case-control study of potential risk factors for LEA found independent associations between low foot transcutaneous tension of oxygen ($TcPO_2$), PVD, absent lower-leg vibratory perception, and LEA (3). Among prospective studies, patients with neuropathy in a health maintenance organization (HMO) were more likely to undergo LEA independent of poor glucose control, but PVD was not studied (4). Among Finnish subjects, high plasma glucose was a risk factor in multivariate models that controlled for peripheral sensory neuropathy and PVD, but associations of peripheral sensory neuropathy and PVD with LEA were not reported (5). In Wisconsin, among individuals followed for 4 years, independent risk factors for LEA included foot ulcers, duration of diabetes, and glycosylated hemoglobin; PVD was not measured (6). Increasing fasting plasma glucose levels and duration of diabetes were both associated with an increased risk of LEA in Nauruans when controlling for risk factors for PVD rather than for PVD itself (7). In Native Americans in Oklahoma, neither foot ulceration nor absent dorsalis pedis pulse were associated with LEA in multivariate model (8).

This prospective study sought to identify risk factors for LEA with an emphasis on lower-extremity neuropathy, vasculopathy, and ulcers. This study also tested whether ulcers were associated with ipsilateral LEA and, by taking advantage of the prospective design, estimated the incidence of LEA.

RESEARCH DESIGN AND METHODS

Study population

The Seattle Diabetic Foot Study is a prospective investigation designed to assess the incidence of and risk factors for lower-extremity complications in U.S. veterans with diabetes. Diabetes was defined by physician diagnosis or current treatment with hypoglycemic medication. Diabetes type was based on an algorithm that incorporated treatment type, age at onset, family history of diabetes, BMI, and history of ketoacidosis. Patients eligible for the study were outpatients followed in the general internal medicine clinic of Veterans Affairs (VA) Puget Sound, WA. In 1988, of 4,211 total outpatients, 1,040 (25%) had diabetes. Excluded from the study were patients who were too ill to participate (n = 40), patients

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Received for publication 16 November 1998 and accepted in revised form 25 February 1999.

Abbreviations: AAI, ankle arm index; DP, dorsalis pedis; HMO, health maintenance organization; HR, hazard ratio; LEA, lower-extremity amputation; PT, posterior tibialis; PVD, peripheral vascular disease; RR, relative risk; $TcPO_2$, transcutaneous tension of oxygen; VA, Veterans Affairs.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

who could not walk 50 feet (n = 71), and patients who were unable (n = 10) or declined (n = 143) to consent but not patients with previous LEA (n = 51). The remaining 776 patients were included in the study. Patients were followed for a median of 3.3 years (0–5.8 years) for a total of 2,305 patient-years.

Data collection

At entry into the study, participants underwent an interview, a physical examination, and laboratory testing. The interview included past and present symptoms, signs, and physician diagnoses of diabetic, foot, and vascular complications. Analyses of blood included measurements of glycosylated hemoglobin, albumin, leukocytes, hematocrit, and creatinine. Physical examination included assessment of peripheral sensory neuropathy, palpation of posterior tibialis (PT) and dorsalis pedis (DP) pulses, observation of stance and gait, examination of edema and ulcers, and measurement of partial pressure of oxygen at the skin surface (transcutaneous oximetry [$TcPO_2$] radiometer; Radiometer A/S, Copenhagen) and with the ankle arm index (AAI). A nurse practitioner performed the examinations, and a trained neurovascular technician performed the AAI and $TcPO_2$ determinations.

Definition of lower-extremity conditions

On the basis of the information obtained during the examination, peripheral sensory neuropathy was defined as insensitivity to the 10-g Semmes-Weinstein monofilament at any one of nine sites (eight plantar, one dorsal) on either foot. PVD was defined in one of three ways: absent or diminished DP and PT pulses to palpation in the same limb, an AAI $\leq$0.8 in either foot (calculated as the higher of the DP or PT arterial systolic Doppler blood pressure divided by the higher brachial arterial Doppler blood pressure in both arms), or $TcPO_2$ $\leq$50 mmHg in either foot measured at 44°C on the dorsum of the foot. The cutoff of 0.8 for the AAI is based on a previous study (9), whereas the value of $\leq$50 mmHg for $TcPO_2$ is between values used in a previous study (10). An ulcer was defined as history of a lower-extremity full-thickness skin defect that did not heal after 14 days. LEA was defined as surgical removal of part of a lower extremity. Heel pronation and supination (versus neutral) was determined as being absent or present during observation of gait. History of calluses, blisters, corns, and infection of a blister, ulcer, or open sore on the feet or legs in the year before study entry was determined during the interview.

Time to first LEA during follow-up (n = 30) or to censoring that included death (n = 124), withdrawal (n = 102), moving away (n = 32), changing clinics (n = 53), or alive without amputation (as of 21 August 1996) (n = 435) was calculated from the date of entry into the study (from 26 October 1990 to 14 July 1994).

Analysis of potential risk factors that were identified from the literature or were deemed to have a plausible association with LEA was performed with univariate Kaplan-Meier survival curves and the log-rank test. Variables not satisfying the proportional hazards assumption were evaluated by the Breslow-Wilcoxon test (11). Multivariate proportional hazard analyses were performed to evaluate the independent contribution of a variable deemed significant in univariate analysis at the 0.1 level of statistical significance. Too few LEAs occurred during follow-up to test all of the variables that met this criterion with multivariate analysis; therefore, independent variables that were considered in advance to be highly correlated were not simultaneously included in the model. Hazard ratios (HRs) and 95% CIs from proportional hazards model coefficients were calculated. The HR is an estimate of the risk associated with the presence of a given variable while considering its association with all other variables in the model. Age, duration of diabetes, and percentage of glycosylated hemoglobin were categorized into tertiles based on the distribution among all patients. To assess statistical interaction between PVD as defined by the AAI, pulses, $TcPO_2$, and peripheral sensory neuropathy, the product of the two was included in a model containing both covariates (12) and then, to assess its magnitude, by creating an indicator variable (13).

To assess the association between ulcers and ipsilateral LEA, a paired case-control analysis was performed by using a within-subject matched analysis wherein the case was defined as the amputated lower extremity, and the control was the nonamputated extremity (14). The odds ratio and 95% CIs were calculated based on discordant pairs (15,16).

Major LEAs were below- and above-the-knee amputations, and minor LEAs were all amputations distal to these. Major and minor LEAs were compared regarding AAI and neuropathy, given that the small number of patients who experienced these events precluded multivariate analysis.

Incidence rates were calculated as the number of first amputations during the study per total patient-years of follow-up. Age-adjusted incidence rates were calculated for men and are directly standardized to the 1991 U.S. male diabetic population based on the National Health Interview Survey (17).

RESULTS

Characteristics of study population

Study subjects were predominantly men (98.2%) and white (78%) with a median age of 65 years (range of 28–91 years). A total of 93% of patients had type 2 diabetes, and 47% of those were treated with insulin. The median duration of diabetes was 9 years.

Univariate analyses

During follow-up, 30 patients underwent surgery for LEA. Neither age nor race was associated with subsequent amputation risk. Individuals who had an LEA during follow-up were more likely ($P < 0.1$) to have had a previous LEA, a previous lower-extremity ulcer, diabetes of longer duration, and treatment with insulin (Table 1). History of congestive heart failure was associated with an increased risk of LEA (P = 0.04, Breslow-Wilcoxon test), but history of stroke was not (P = 0.55). On the basis of examination, sensory neuropathy, presence of heel pronation or supination, absence of posterior tibial and dorsalis pedis pulses in the same limb, an AAI $\leq$0.8, and $TcPO_2$ $\leq$50 mmHg were more common in patients who underwent LEA and were also more likely to have had self-reported foot blisters, infected ulcers or sores, a history of arterial bypass to the leg, and orthopedic shoes. These patients were not more likely to have walked barefoot or have calluses, fissures, cuts, or corns. Not associated with LEA were glycosylated hemoglobin at study entry, diabetes type (type 1 vs. type 2), or smoking (either current smokers or patients who had ever smoked). The site of amputation is presented in Table 2.

Multivariate analyses

Three models incorporating different measures of PVD are shown in Table 3. Former amputation, lower-extremity ulcers, PVD, peripheral sensory neuropathy, and treatment with insulin were associated with an increased risk of LEA when controlling for

Table 1—*Characteristics at study entry of population, patients who underwent LEA, and patients who did not undergo LEA*

	LEA	No LEA	*P* value*
Related to diabetes			
Duration of diabetes			0.0057
≤ 5 years	3 (10)	260 (35)	
> 5 and ≤ 14 years	11 (37)	257 (34)	
> 14 years	16 (53)	229 (31)	
Treatment with insulin			0.0001
No	5 (17)	403 (54)	
Yes	25 (83)	343 (46)	
Diabetes type 1			0.96†
No	28 (93)	697 (93)	
Yes	2 (7)	49 (7)	
Lower-extremity history			
History of previous amputation			<0.0001
No	22 (73)	703 (94)	
Yes	8 (27)	43 (6)	
History of ulcer			0.0001
No	15 (50)	613 (82)	
Yes	15 (50)	133 (18)	
Arterial bypass to leg			0.0008
No	25 (83)	702 (94)	
Yes	5 (17)	44 (6)	
Smoking			0.6093
Never	4 (13)	119 (16)	
Ever	26 (87)	627 (84)	
History of infection in the lower extremity			0.0000
No	17 (57)	684 (92)	
Yes	13 (43)	58 (8)	
History of blisters in the foot			0.0407
No	22 (73)	656 (88)	
Yes	8 (27)	90 (12)	
Wears orthopedic shoes			0.0038
No	19 (63)	625 (84)	
Yes	11 (37)	120 (16)	
Glycosylated hemoglobin (%)			0.4167
≤ 9.4	7 (23)	258 (35)	
9.4–12.6	14 (47)	252 (34)	
≥ 12.6	9 (30)	231 (31)	
Creatinine, serum (mg/dl)			0.0662
≤ 1.3	15 (50)	464 (62)	
> 1.3	15 (50)	280 (38)	
Clinical measures in lower extremity			
Peripheral sensory neuropathy			0.0006
Neither lower extremity	5 (17)	376 (51)	
Either lower extremity	25 (83)	364 (49)	
AAI ≤ 0.8			0.0001
Neither lower extremity	14 (48)	488 (74)	
Either lower extremity	15 (52)	173 (26)	
$TcPO_2$ ≤ 50 mmHg			0.007
Neither lower extremity	7 (24)	346 (52)	
Either lower extremity	22 (76)	323 (48)	
DP and PT pulses			0.0001
Both pulses normal or one pulse absent or diminished in both limbs	15 (52)	508 (77)	
Both pulses absent or diminished in one or both limbs	14 (48)	153 (23)	

Table 1 *(continued from 1031)*

	LEA	No LEA	*P* value*
Heel pronation or supination			0.024
No	17 (57)	557 (75)	
Yes	13 (43)	186 (25)	
Lower-extremity edema on exam			0.0082
Neither extremity	15 (50)	461 (62)	
One extremity	4 (13)	27 (3.6)	
Both extremities	11 (37)	258 (35)	

Data are *n* (%). *Difference between groups by log-rank test unless indicated by †(Breslow-Wilcoxon test).

duration of diabetes, which itself did not increase risk. Peripheral sensory neuropathy achieved significance in the model in which PVD was measured by $TcPO_2$.

Interaction between PVD and neuropathy

The coefficient associated with the product of absent or diminished DP and PT pulses and neuropathy in a model was negative and of borderline statistical significance ($P = 0.051$). In a multivariate model, relative to a reference HR of 1.0 for individuals without diminished or absent pulses and without neuropathy, absent or diminished pulses in either leg but without neuropathy were associated with an HR of 20.5, neuropathy alone (without absent or diminished pulses) was associated with an HR of 9.3, and absent or diminished pulses and neuropathy together were associated with an HR of 19.0. The interactions between an AAI ≤0.8 or poor $TcPO_2$ and neuropathy were not significant at $P = 0.068$ and $P = 0.327$, respectively.

Table 2—*Site and side of amputations*

Amputation site	Right	Left	Total
Great toe	1	1	2 (6.7)
Other toes	7	3	10 (33.3)
Midfoot	3	1	4 (13.3)
Syme	1	1	2 (6.7)
Below knee	4	5	9 (30.0)
Above knee	1	2	3 (10.0)
Hip disarticulation	0	0	0 (0.0)
Total	17	13	30 (100)

Data are *n* or *n* (%).

Ipsilateral ulcers and amputation

All patients who had an LEA, but only 27% of patients who did not, had a preceding ulcer at some time either before or during the study, which suggests a strong association between ulcer and LEA. The paired case-control analysis included 20 patients without LEA before study entry who had an LEA during follow-up, and whose first ulcer during follow-up was unilateral. Of the 20 subjects, 17 developed an ipsilateral LEA, and 3 developed a contralateral LEA. The odds ratio associated with first ulcer for a subsequent ipsilateral amputation was 5.7 (CI 1.6–30.2).

Major versus minor amputation

Among patients who had no history of LEA before study entry, similar proportions of patients with minor and major amputations had a history of ulcers at study entry. In univariate proportional hazards models, when comparing individuals with either a major or minor LEA to individuals without LEA, an AAI ≤0.8 was a not significantly associated with minor amputation (RR = 2.6, CI 0.7–9.3), although it was a risk factor for major amputation (RR = 5.8, CI 1.6–20.4). By contrast, peripheral sensory neuropathy at study entry was a risk factor for subsequent minor amputation (RR = 5.4, CI 1.2–24.7) but not major amputation (RR = 3.4, CI 0.7–16.3).

Incidence rates

The crude incidence rate for LEA was 13.4/1,000 patient-years. Of the patients, 51 had an LEA before entry into the study. Excluding these patients, 22 patients had an LEA in 2,175 patient-years of follow-up. The incidence was 10.1/1,000 patient-years. Total (crude) and age-stratified rates for men are presented in Table 4 and are compared with other studies in Table 5.

CONCLUSIONS — This prospective study has shown that peripheral sensory neuropathy and PVD are independent risk factors for LEA in patients with diabetes. This study identified additional clinical risk factors including former amputation, treatment with insulin, and lower-extremity ulcers, particularly if the

Table 3—*Multivariate proportional hazards models with various measures of PVD*

Variable	AAI model	$TcPO_2$ model	Pulses model
Former amputation	3.3 (1.4–8.1)	3.4 (1.4–8.1)	3.0 (1.2–7.4)
Measure of PVD			
AAI ≤0.8 in either lower extremity	2.9 (1.3–6.2)	—	—
$TcPO_2$ ≤50 mmHg in either foot	—	3.0 (1.3–7.1)	—
Absent or diminished DP and PT pulse in either limb	—	—	3.0 (1.4–6.5)
Lower-extremity ulcer (ever)	2.5 (1.1–5.4)	2.5 (1.1–5.4)	2.1 (1.0–4.6)
Peripheral sensory neuropathy	2.2 (0.8–6.2)	2.9 (1.1–7.8)	2.5 (0.9–6.8)
Diabetes treatment with insulin	3.3 (1.2–9.2)	3.0 (1.1–8.6)	3.3 (1.2–9.3)
Duration of diabetes (each year)	1.00 (0.97–1.04)	1.00 (0.98–1.05)	1.01 (0.97–1.05)
n available for analysis	689	693	685

Data are HRs (95% CI).

Table 4—*Number of amputations, patient-years at risk, and incidence rate per 1,000 patient-years of follow-up among men*

Age (years)	Number of amputations	Patient-years of follow-up (men)	Incidence	Number of first amputations*	Patient-years of follow-up in patients*	Incidence
<45	1	92.2	10.8	1	92.2	10.8
45–64	8	932.1	8.6	5	874.8	5.7
65–74	19	1,050.8	18.1	14	981.6	14.3
>75	2	257.2	7.8	2	249.7	8.0
Total unadjusted (men only)	30	2,332.3	12.9	22	2,198.3	10.0
Total age-standardized (men only)†			11.3			9.2

No amputations occurred in women. *Excludes those with previous amputations. †Age adjusted to U.S. male population with diagnosed diabetes in 1991.

ulcer appears on the same side as the eventual LEA.

The greater HR associated with measures of PVD compared with neuropathy suggests that the risk associated with PVD is greater than that for neuropathy, although this conclusion remains speculative because of the imprecision of the CIs. PVD may mitigate the effect of sensory neuropathy or vice versa, and, possibly, once a patient has PVD, neuropathy does not further increase risk. These findings may be because patients with both conditions received better care or because surgeons were reluctant to operate on patients who were possibly poor surgical risks. A delay in surgery could cause an underestimation in the HRs associated with PVD and neuropathy in patients with both conditions. The RRs of PVD and neuropathy were elevated regarding both major or minor amputation, and a larger study is required to adequately evaluate major and minor amputation separately.

Whatever the means of measurement, PVD was associated with a threefold increased risk for LEA. Palpation of absent or weak lower-extremity peripheral pulses performs well diagnostically compared with other measures of PVD in diabetes (18), even though palpation can vary between observers (19). Poor $TcPO_2$ has previously been shown to predict amputation in patients with severe PVD, but the contribution of ulcers or neuropathy was not evaluated (20). Low $TcPO_2$ measured shortly before amputation was associated with LEA in patients with diabetes (3).

The finding of increased risk among patients with former amputation or ulcers is consistent with previous studies (6,21). Most ulcers in this study were likely neu-

Table 5—*Incidence per 1,000 of LEA in patients with diabetes from selected studies*

Population	Reference no.	Period	Incidence in men	Incidence in women	Incidence total	Units (denominator)	Age adjusted
Seattle, WA	Current study	1988–1996	11.3	—	—	Patient-years	Yes
Arizona (Pima)	29	1972–1984	15.3*	7.1*	13.7	Patient-years	Yes
Alaska (Alaska natives)	46	1986–1992	—	—	5.1	Patient-years	Yes
Oklahoma (Indians)	8	1987–1991	26.1	13.5	18.0	Patient-years	No
Nauru	7	1982–1994	11.3	6.3	8.4	Patient-years	No
U.S.	37	1980–1988	—	—	7.1	Estimated diabetic population	Yes
California (whites)	30	1991	—	—	5.6	Estimated diabetic population	Yes
California (African-American)	30	1991	—	—	9.5	Estimated diabetic population	Yes
Rhode Island, Maine, South Carolina, Illinois, Ohio, and Minnesota	38	1978	7.7	5.4	—	Estimated diabetic population	Yes
Leicester, England (white)	39	1980–1985	1.8	1.1	—	Estimated diabetic population	No
Leicester, England (South Asians)	39	1980–1985	0.7	0.0	—	Estimated diabetic population	No
Newcastle-upon-Tyne, England	40	1989–1991	—	—	5.7	Estimated diabetic population	No
Tayside, Scotland	41	1980–1982	—	—	10.1	Estimated diabetic population	No
Tayside, Scotland	42	1993–1994	—	—	2.5	Patient-years	Yes
Kuopio Province, Finland	43	1978–1984	3.5	2.4	—	Estimated diabetic population	Yes
Leverkusen, Germany	44	1990–1991	—	—	5.4	Estimated diabetic population	No
Denmark	45	1982–1993	—	—	1.1	Estimated diabetic population	No

*Calculated from reference.

ropathic in origin because, of patients who reported ever having had an ulcer, 64% had neuropathy at study entry compared with 47% of patients who reported never having an ulcer ($P < 0.001$). In contrast, there was no significant difference in the prevalence of PVD (30 vs. 23%) among patients who reported ever having an ulcer. However, the distinction between neuropathic and vascular ulcers is not a clear one because neuropathy may contribute to foot ulceration via effects on the microcirculation (2). Neuropathy, but not vasculopathy, in patients with diabetes was a risk factor for ulcers (22), whereas in other studies both poor $TcPO_2$ and insensitivity to the 5.07 monofilament have been associated with an increased risk of ulceration (10,23). If all ulcers were neuropathic in this study, then interpretation of neuropathy and ulcers within the same model could be problematic (24). It is plausible that neuropathy may precipitate an ulcer and vasculopathy may inhibit its healing. In support of this possibility, low DP blood pressure and low $TcPO_2$ measured adjacent to an ulcer predicted delayed wound healing (25), and PVD measured by angiography was associated with an increased risk of subsequent LEA in patients with diabetic ulcers (26). In this study, there was no evidence that the risk of LEA associated with ulcers differed depending on $TcPO_2$ (not shown); however, $TcPO_2$ was not measured at the ulcer site. A larger study is necessary to address this issue.

Regarding diabetes-specific factors, treatment with insulin, but not glycosylated hemoglobin level measured at entry, was independently associated with risk of LEA independent of duration of diabetes. In prospective studies, treatment of diabetes with insulin was not associated with an increased risk of LEA independent of duration of diabetes in one report (4), whereas use of insulin, duration of diabetes, and fasting plasma glucose independently increased the risk in another (8). Among Nauruans, both duration of diabetes and fasting plasma glucose independently increased the risk of amputation (7). Treatment with insulin may reflect more severe diabetes or hyperglycemia itself.

Not only the presence, but also the absence, of risk factors are causes for speculation. The absence of the association for hyperglycemia existed even when HbA_{1c} was modeled as a continuous variable. Treatment with insulin, which was associated with an increased risk of LEA in this study, is likely to have been a marker for hyperglycemia before entry into the study. Age was not a risk factor in this study, even in univariate analyses, despite age being associated with both neuropathic ulcers (27) and PVD (28) among individuals with diabetes. However, age has not been associated with LEA in other studies (6,29). By using data from the state of California, the incidence of LEA was not higher in people aged >75 years than in people aged 65–74 years (30). The observation of the lowest rate among the oldest patients in this study may reflect relatively good health in those who live to that age or possibly the reluctance by surgeons to operate on older patients. Smoking (either current smokers or patients who had ever smoked) was not a risk factor for LEA in this study, in a study of a similar population (3), or in diabetes clients of an HMO (4) in multivariate analyses, although it is a risk factor for PVD (31,32). Former smokers may have quit because of the development of macrovascular disease, which subsequently increased the risk for amputation. Among diabetic individuals in Wisconsin, smoking increased the risk of LEA, but PVD was not considered (6). However, in this study, smoking was not a risk factor for LEA even in univariate analysis. Interpretations regarding smoking must consider the high proportion of individuals in this study who at any time have smoked (84%), which makes it difficult to assess the contribution of this exposure given the infrequency of never-exposed subjects.

The number of amputations observed in this study prohibited multivariate assessment of all potential risk factors or even all those significant in univariate analysis, and possibly some of these would have been independently associated with LEA. Regarding potential biases, misclassification of LEA was unlikely because the definition was unambiguous. Misclassification of foot problems based on interview may have occurred because a high proportion of patients with ulcers are unaware of their presence (33). This bias would act to underestimate the risk associated with ulcers. Potential confounders related to the decision to amputate among surgeons were not evaluated. The possibility that nonblinded examiners could be more likely to diagnose PVD in patients with a former LEA (a risk factor for LEA) is unlikely because $TcPO_2$, which would seem less subject to observer bias, independently predicted LEA. Because young, female, nonwhite, and type 1 diabetic patients comprised only a small proportion of this patient population, these results may not be generalizable to these groups.

This study provides information for primary care and specialist practitioners to identify diabetic patients at high risk for amputation. All measures in this study, with the exception of $TcPO_2$, are easily obtained. This study supports the initiation of a trial of improved vascular perfusion in individuals with diabetic foot ulcers as a means to reduce the incidence of amputation. Short of preventing diabetes itself, this study implies that prevention of foot lesions and even neuropathy in individuals with diabetes (34,35) may markedly reduce the incidence of LEA (36).

Acknowledgments — This research was supported by VA Merit Review Rehabilitation Research and Development Grant A318–3RA and the VA Epidemiologic Research and Information Center (ERIC) Grant 97–010 (Seattle, WA).

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