Risks of Nontraumatic Lower-Extremity Amputations in Patients with Type 1 Diabetes

A population-based cohort study in Sweden

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OBJECTIVE — The purpose of this study was to estimate the risks of nontraumatic lower-extremity amputations (LEAs) in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — We identified 31,354 patients with type 1 diabetes (15,001 women and 16,353 men) in the Swedish Inpatient Register between 1975 and 2004. The incidence of nontraumatic LEAs was followed up until 31 December 2004 by cross-linkage in the Inpatient Register and linkage to the Death and Migration registers. Poisson regression modeling was used to compare the risks of nontraumatic LEAs during different calendar periods of follow-up, with adjustment for both sex and attained age at follow-up. Standardized incidence ratios (SIRs) were used to estimate the relative risks (RRs) with the age-, sex-, and calendar period–matched general Swedish population as reference. The cumulative probability of nontraumatic LEAs was calculated by the Kaplan-Meier method.

RESULTS — In total, 465 patients with type 1 diabetes underwent nontraumatic LEAs. The risk was lower during the most recent calendar period (2000–2004) than during the period before 2000 (RR 0.6 [95% CI 0.5–0.8]). However, even in this most recent period, the risk for nontraumatic LEAs among these relatively young patients was 86-fold higher than that in the matched general population (SIR 85.8 [72.9–100.3]). By age 65 years, the cumulative probability of having a nontraumatic LEA was 11.0% for women with type 1 diabetes and 20.7% for men with type 1 diabetes.

CONCLUSIONS — Although the risks appeared to have declined in recent years, patients with type 1 diabetes still have a very high risk for nontraumatic LEAs.

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U lceration of the foot is the most common first indicator of impending nontraumatic lower-extremity amputations (LEAs) related to diabetes, and it has been estimated worldwide that one lower limb is amputated every 30 s as a consequence of this condition. Of all nontraumatic LEAs, 50–70% are associated with diabetes (1). Diabetic foot ulceration involves a complex underlying pathophysiology and a multifactorial approach to care, including preventive foot care, aggressive management of acute foot ulceration, control of infections, and early recognition of vascular disease, which are all of major importance in this context (2,3). In addition to reducing quality of life and enhancing morbidity, disability, and premature mortality (4,5), diabetic foot complications are a considerable financial burden on society and individual patients (6), accounting for ~20% of the total expenditure on health care for patients with diabetes (1).

The incidence of nontraumatic LEAs as a consequence of diabetes is considered to be a key indicator of the quality of foot care for such patients (7). In 1989, the World Health Organization and International Diabetes Federation initiated a joint program called the Saint Vincent Declaration for improving the care of patients with diabetes (8). The goals set forth included a >50% reduction in major nontraumatic LEAs caused by diabetes. It is unclear whether this goal has been attained in the case of type 1 diabetes, as most relevant epidemiological studies reported have been concerned with patients with type 2 diabetes or a mixture of type 1 and type 2 diabetic patients (9–11). Therefore, the aim of this register-based study involving a large cohort was to obtain an estimate of the risk of nontraumatic LEAs in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — This study was approved by the Regional Ethics Committee at the Karolinska Institutet.

In 1964/1965, the National Board of Health and Welfare established the Swedish Inpatient Register and different counties joined on different occasions thereafter until nationwide coverage was attained in 1987. By 1977, 73% of all Swedish counties were included (12). Each record in this register corresponds to one hospital admission and contains, in addition to the patient's national registration number (a unique identifier assigned to all residents of Sweden), the dates of admission and discharge, codes indicating all surgical procedures performed and the diagnosis at the time of discharge. Cohort enrollment started on different dates in the different counties, but in all cases it was at least 2 years after uninterrupted full-coverage registration was achieved in the county. The ICD coding used before the 10th revision in 1997 does not allow us to distinguish between patients with type 1 or type 2 diabetes and, furthermore, even after this date, certain patients

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Table 1—*Characteristics of the patients hospitalized at least once for type 1 diabetes, 1975–2004, Sweden*

	Women	Men	Total
n	15,001	16,353	31,354
Age at enrollment (years)	19.9 ± 11.3	19.6 ± 11.1	19.7 ± 11.1
Mean calendar year at entry	1990	1991	1991
Follow-up duration (years)	13.1 ± 7.6	12.0 ± 7.4	12.5 ± 7.5
Person-years accumulated	196,928	196,206	393,134
Patients with (%)			
Ophthalmic complications*	20.6	16.4	18.4
Diabetic nephropathy†	9.2	8.5	8.8
Neurological complications‡	7.1	7.1	7.1
No. of nontraumatic LEAs§	201	264	465
Amputation above knee	18	11	29
Amputation below knee	82	111	193
Amputation below ankle	101	142	243
Age at diagnosis (years)	45.1 ± 7.6	45.6 ± 8.1	45.4 ± 7.8

Data are means ± SD unless indicated otherwise. *Ophthalmic complications defined by ICD-7 codes 260.20, 260.21, and 260.29, ICD-8 codes 250.01, 250.02, and 250.03, ICD-9 code 250E, and ICD-10 codes E10.3, E11.3, E12.3, E13.3, and E14.3. †Diabetic nephropathy defined by ICD-7 code 260.30, ICD-8 code 250.40, ICD-9 code 250D, and ICD-10 codes E10.2, E11.2, E12.2, E13.2, and E14.2. ‡Neurological complications defined by ICD-7 codes 260.40 and 260.49, ICD-8 code 250.05, ICD-9 code 250F, and ICD-10 codes E10.4, E11.4, E12.4, E13.4, and E14.4. §LEA defined by the operation code: amputation below the ankle was defined by operation codes 8750 or 8760 before 1998 and NHQ16, NHQ17, NHQ12, NHQ13, NHQ14, or NHQ99 afterwards; amputation above the ankle but below the knee was defined by operation codes 8770 or 8771 before 1998 and NGQ19, NHQ09, NHQ11, or NGQ99 afterwards; and amputation above the knee was defined by operation codes 8780 or 8781 before 1998 and NGQ09, NFQ19, or NFQ99 afterwards. Traumatic amputations of the lower-extremity were excluded.

coded as having type 1 diabetes actually had type 2 diabetes that had advanced into a state of insulin dependence. For these reasons, an age of <31 years at the time of index hospitalization for diabetes (even if this date preceded the start of our cohort recruitment) was considered here to be an obligatory criterion for entry into our cohort of patients with type 1 diabetes. Further details concerning how we identified type 1 diabetic patients from the Swedish Inpatient Register have been reported elsewhere (13).

We first identified 31,950 records of patients with a discharge diagnosis of type 1 diabetes. Their records were linked to the Register of Total Population, the Emigration Register, and the Causes of Death Register. These linkages resulted in the exclusion of 42 records for which national registration numbers could not be found in any of the registers, i.e., records without a link to any currently or previously existing individual. Also excluded were 58 patients with amputation before the index hospitalization and 496 patients with other inconsistencies found in the record linkages. Thus, our final cohort consisted of 31,354 patients with type 1 diabetes.

Follow-up

The cohort members were followed from immediately after the index hospitalization for type 1 diabetes until a first hospitalization with a recorded nontraumatic LEA, emigration from Sweden, migration to a county with no or incomplete Inpatient Register coverage, death, or the end of follow-up (31 December 2004), whichever occurred first. Occurrences of nontraumatic LEAs were identified through cross-linkages in the Inpatient Register. Amputations above the knee were defined by operation codes 8780 or 8781 before 1998 and NGQ09, NFQ19, or NFQ99 thereafter. Amputations below the knee were defined by operation codes 8770 or 8771 before 1998 and NGQ19, NHQ09, NHQ11, or NGQ99 thereafter. Amputations below the ankle were defined by operation codes 8750 or 8760 before 1998 and NHQ16, NHQ17, NHQ12, NHQ13,

Table 2—*RRs (95% CIs) for nontraumatic LEAs, according to calendar period at follow-up, sex, and attained age, among patients hospitalized at least once for type 1 diabetes, 1975–2004, Sweden*

	All nontraumatic LEAs		Amputation above knee		Amputation below knee but above ankle		Amputation below ankle	
	Obs*	RR (95% CI)	Obs	RR (95% CI)	Obs	RR (95% CI)	Obs	RR (95% CI)
Calendar period at follow-up								
1975–1999	307	Reference	21	Reference	132	Reference	154	Reference
2000–2004	158	0.6 (0.5–0.8)	8	0.5 (0.2–1.3)	61	0.5 (0.4–0.7)	89	0.7 (0.5–0.9)
Sex								
Male	264	Reference	11	Reference	111	Reference	142	Reference
Female	201	0.7 (0.5–0.8)	18	1.5 (0.7–3.1)	82	0.6 (0.5–0.8)	101	0.6 (0.5–0.8)
Attained age (years)								
<40	126	Reference	12	Reference	37	Reference	77	Reference
40–49	204	9.7 (7.7–12.1)	12	5.8 (2.6–12.9)	94	15.4 (10.5–22.6)	98	7.5 (5.6–10.1)
50–59	121	21.3 (16.5–27.5)	4	7.4 (2.3–23.4)	59	37.1 (24.4–56.5)	58	16.1 (11.3–22.8)
≥60	14	42.9 (24.3–75.6)	1	33.7 (4.0–280.8)	3	34.7 (10.5–114.7)	10	45.9 (23.2–90.9)
P_{trend}		<0.0001		<0.0001		<0.0001		<0.0001

Variables listed in the table were mutually adjusted. *Obs, number of observed nontraumatic LEAs in each category.
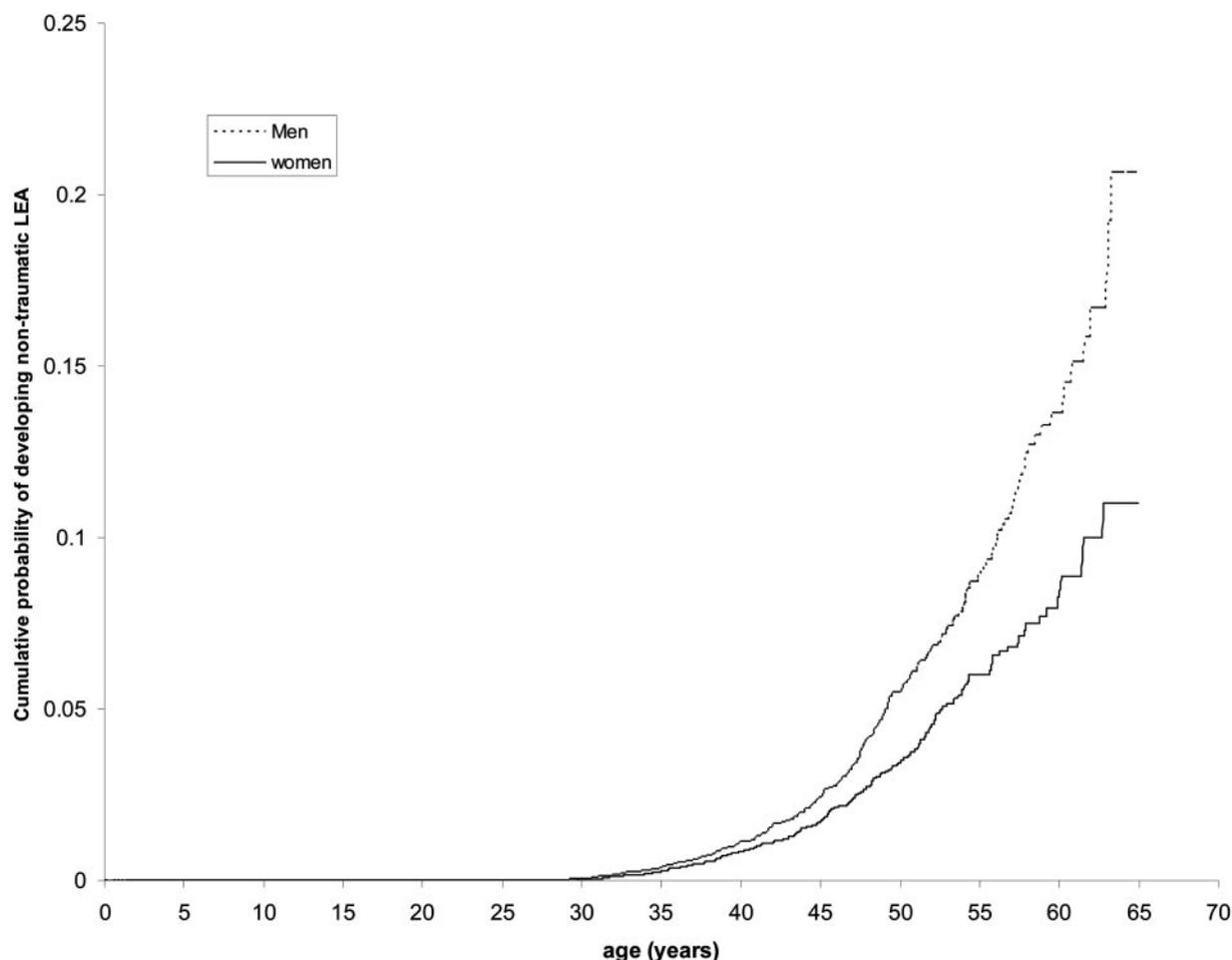
Figure 1—*The cumulative probability of nontraumatic LEA among type 1 diabetic patients, estimated by the Kaplan-Meier method.*

NHQ14, or NHQ99 thereafter. Traumatic LEAs were excluded from our analysis.

Statistical analyses
To compare the risk for nontraumatic LEAs during different calendar periods of follow-up with adjustment for sex and attained age at follow-up, multivariable Poisson regression models were fitted with the logarithm of the number of person-years observed as the offset, assuming multiplicative relationships between the outcome and the explanatory variables. Pearson's χ^2 statistic was used to estimate the goodness of fit for the multivariable Poisson regression models. To test the trend of the relative risks (RRs) associated with attained age at follow-up, the categorical variable of attained age-groups at follow-up was treated as a semicontinuous variable in the regression model.

Standardized incidence ratios (SIRs), the ratios of the observed to the expected numbers of first hospitalization for nontraumatic LEAs, were used as a measure of the RRs. The corresponding 95% CIs

were calculated by assuming that the number of observed events followed a Poisson distribution (14). To calculate the expected rates, we first counted the numbers of first occurrence of nontraumatic LEA among the general population by age (in 5-year groups), sex, and 5-year calendar period in every county in Sweden. Because a large proportion of all nontraumatic LEAs among young patients are attributable to type 1 diabetes, we then subtracted the stratum-specific outcome number of observed events in our cohort from the number of nontraumatic LEAs in the respective stratum in the general population. Stratum-specific incidence rates were calculated by dividing the number of nontraumatic LEAs in each stratum by the corresponding general population count. The expected number of nontraumatic LEAs in our cohort was derived by multiplying the observed number of person-years in the cohort by the age-, sex-, and calendar period–matched incidence rates.

The cumulative probability of development of a nontraumatic LEA by age

65 years was calculated separately for women and men using the Kaplan-Meier method. In addition, the log-rank test was applied to test the statistical significance of any differences observed between groups. All statistical analyses were performed with SAS software (version 9.1; SAS Institute, Cary, NC).

RESULTS — The 15,001 women and 16,353 men in our cohort, with a mean age of 19.7 years at entry, exhibited no obvious differences with respect to baseline characteristics (Table 1). Of our cohort members, ~18% exhibited diabetic retinopathy, 9% nephropathy, and 7% neuropathy recorded at any given point. On average, our cohort members were followed for 12.5 years, yielding a total of 393,134 person-years at risk. A total of 465 cohort members underwent nontraumatic LEAs: 29 above the knee, 193 below the knee but above the ankle, and 243 below the ankle. The mean age at non-

traumatic LEAs was 45.4 years (range 25.2–69.7 years).

The risk of nontraumatic LEAs for type 1 diabetic patients was 40% lower (95% CI 20–50%) during the most recent calendar period of follow-up (2000–2004) than that during the previous calendar period. Women demonstrated a lower risk than men (RR 0.7 [95% CI 0.5–0.8]), and the RR clearly increased with increasing attained age at follow-up (Table 2). Analyses based on the site of amputations revealed similar patterns, except that women appeared to have a higher risk for amputation above the knee, although this difference was not statistically significant.

In comparison with the age-, sex-, and calendar period–matched general population, patients with type 1 diabetes demonstrated notably elevated risks for nontraumatic LEAs. For example, during the most recent calendar period of follow-up (2000–2004), the SIR was as high as 85.8 (95% CI 72.9–100.3) for all nontraumatic LEAs: 19.6 (8.5–38.6) for amputation above the knee, 86.8 (66.4–111.5) for amputation below the knee but above the ankle, and 121.8 (97.9–149.9) for amputation below the ankle.

Figure 1 illustrates the cumulative probability of development of nontraumatic LEAs among patients with type 1 diabetes, as estimated by the Kaplan-Meier method. As we can see, this probability was almost negligible for both men and women before age 30 years, increased in a similar manner for both sexes during the next decade of life, but increased more rapidly in men after age 40 years. Thus, by age 65 years, the cumulative probability of nontraumatic LEA was 11.0% for women and 20.7% for men ($P_{\text{log-rank}} < 0.01$).

CONCLUSIONS — This investigation revealed that patients with type 1 diabetes have substantial absolute and relative risks for nontraumatic LEAs. As many as 1 of 10 women and 1 of 5 men with this disease may have undergone a nontraumatic LEA by age 65 years. The clear reduction in the risk of nontraumatic LEAs among patients with type 1 diabetes in the most recent calendar period of follow-up might be due to the introduction of a national program for the prevention and treatment of foot ulceration in patients with diabetes (15), although a longer period of follow-up is required to confirm this trend.

Our finding that men with type 1 diabetes have higher risks for nontraumatic LEAs than women with type 1 diabetes is consistent with previous reports (9, 11,16). This more pronounced cumulative risk in men may reflect several factors, including the fact that smoking is more common among men (17) and that wounds heal more efficiently in women as a consequence of their expression of the estrogen receptor-β (18,19).

The strengths of the present study include its cohort design, the use of medical information recorded by doctors rather than self-reports by patients, and the virtually complete follow-up due to the requirement for hospital care for amputations and high coverage of the present cohort by the Swedish Inpatient Register. Nonetheless, this investigation also has certain limitations. First, we did not have access to information concerning treatment and the state of metabolic control of our patients. Second, patients with type 1 diabetes who had never been hospitalized were not identified, and failure to include these patients would lead to an overestimation of the risk for nontraumatic LEAs in our patients with type 1 diabetes. However, because most of such patients in Sweden are highly likely to be hospitalized at the time of diagnosis in Sweden, in accordance with the National Program for Diabetes Care (20,21), the proportion missed is considered to be very small indeed. Third, although we have subtracted type 1 diabetes–related cases of nontraumatic LEAs in our calculation of the background rates, some of these cases might have been missed, especially during the earlier calendar periods of follow-up. This false inflation of background rates in the general population might have caused the underestimation of the actual RRs for nontraumatic LEAs among our patients.

In summary, even though our data do suggest that the risk of nontraumatic LEA among patients with type 1 diabetes has attenuated in recent years, patients diagnosed with this disease before age 31 years nonetheless have strikingly high absolute and relative risks of nontraumatic LEAs. The apparent decline in the risks indicates that recent preventive efforts have been effective, but the findings documented here emphasize the need for the unrelenting application of measures designed to prevent nontraumatic LEAs early in the course of type 1 diabetes.

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