Mortality and Hospitalization in Patients After Amputation

A comparison between patients with and without diabetes

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OBJECTIVE — We sought to compare the risk of mortality and hospitalization between patients with and without diabetes following incident lower-extremity amputation (LEA).

RESEARCH DESIGN AND METHODS — We performed a retrospective data-linkage review of all incident amputations between 1 January 1992 and 31 December 1995. Patients were categorized according to their diabetes status. Follow-up for mortality was until 1 January 2005 and until 31 March 1996 for hospitalization.

RESULTS — Of 390 major-incident LEAs performed during the study period, 119 (30.5%) were in patients with diabetes and 271 (69.5%) were in nondiabetic subjects. The median time to death was 27.2 months in patients with diabetes compared with 46.7 months for patients without ($P = 0.01$). Diabetic subjects had a 55% greater risk of death than those without diabetes. The risk of developing congestive cardiac failure with diabetes was 2.26 (95% CI 1.12–4.57) and of further amputation was 1.95 (1.14–3.33) times that of a patient without diabetes after incident LEA.

CONCLUSIONS — After LEA, patients with diabetes have an increased risk of death compared with nondiabetic patients. Efforts should be made to minimize these risks with aggressive treatment of cardiovascular risk factors and management of cardiac failure.

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Foot problems, including ulceration and amputation, account for more hospital admissions for patients with diabetes than any other long-term complication (1). Ulceration is usually precipitated by trauma in the presence of neuropathy and/or ischemia. Foot ulceration and amputation can be prevented by up to 78% with early identification and effective management (2). Despite calls by the World Health Organization and the U.S. government to reduce lower-limb amputation (3,4), it remains a major burden on health care resources with high postoperative mortality, a high rate of secondary amputation, and prolonged inpatient stay.

A significant number of patients with diabetes will have multiple hospital admissions following surgery, further episodes of foot ulceration, and further amputation, increasing the total cost of care. Many of these patients have peripheral vascular disease (PVD) and/or peripheral neuropathy in the contralateral limb. They also have coexisting risk factors for micro- and macrovascular disease.

In a previous retrospective cohort study (5), we compared incidence rates of lower-extremity amputations (LEAs) in patients with diabetes with a nondiabetic population. The established adjusted incidences of LEA in patients with diabetes was 248 per 100,000 person-years and for nondiabetic patients, 20 per 100,000 person-years. Patients with diabetes from Tayside, Scotland, thus had a 12.3-fold increased risk of amputation compared with nondiabetic residents (5).

Previous studies have compared mortality and morbidity following LEA in diabetic and nondiabetic patients (6–9), but accurate data are required on the short- and long-term outcome of patients following diabetes-related LEA in Tayside. The aim of this study was to define the incidence of death and macrovascular complications following amputation in diabetic and nondiabetic subjects in Tayside.

RESEARCH DESIGN AND METHODS

— This study is a retrospective cohort study in a fixed population that comprised all residents of Tayside, Scotland, who were registered with a Tayside general practitioner in January 1992 and who were still residing in Tayside as of 31 March 1998 or had died during the intervening period. Patients leaving the area during the study period were excluded from the analysis.

Every patient who is registered with a general practitioner in Scotland is allocated a unique community health number (CHN). The CHN is used as the patient identifier in all health care activities in Tayside. This is a 10-digit integer; the first 6 digits represent the patients date of birth, and the last 4 are a unique identifying number. Every resident of Tayside who is registered with a general practitioner appears in the centrally held, continuously updated, computerized record called the Community Health Master Patient Index. This file contains data on address, postcode, practitioner, deceased individuals, and date of death.

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Abbreviations: CHN, community health number; DARTS, Diabetes Audit and Research in Tayside Scotland; LEA, lower-extremity amputation; MEMO, Medicines Monitoring Unit; OPCS4, Office for Population Censuses and Surveys; PVD, peripheral vascular disease; SMR1, Scottish Morbidity Record 1.

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

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Table 1—*Subject characteristics by diabetes status*

	With diabetes	Without diabetes	*P* value
Age (years)	69.9 ± 11.8	70.6 ± 15.8	NS
Male	74 (62.2)	119 (43.9)	0.0009
Carstairs score			
1	9 (7.8)	16 (6.0)	
2	17 (14.7)	42 (15.9)	
3	30 (25.8)	70 (26.4)	
4	26 (22.4)	58 (21.9)	
5	11 (9.5)	26 (9.8)	
6	23 (19.8)	53 (20.0)	NS
Index amputation			
Major	66 (55.5)	159 (58.8)	
Minor	53 (44.5)	112 (41.2)	NS

Data are means ± SD or *n* (%). All tests are χ^2 except age (*t* test). NS, not significant.

Thus, the demographic breakdown of the Tayside population, death rate, and patient migration can be easily analyzed.

Patients with diabetes were identified using the Diabetes Audit and Research in Tayside Scotland (DARTS)/Medicines Monitoring Unit (MEMO) Collaboration. DARTS has been described in detail elsewhere (10). In brief, electronic record linkage of eight data sources has created a diabetes information system for Tayside. Data sources include all hospital diabetes clinics, all encashed prescriptions for diabetes medication and monitoring equipment as ascertained by the MEMO (11), hospital discharge data, the community-based mobile diabetic eye screening facility (12), and all HbA_{1c} and plasma glucose results from the regional biochemistry database. Every one of these data sources are linked using the patients by CHN validation of our methodology, showing DARTS to be 97% sensitive with a positive predictive value of 97% for the diagnosis of diabetes (10).

A LEA was defined as the complete loss in the transverse anatomical plane of any part of the lower limb. The primary data source was the Scottish Morbidity Record 1 (SMR1) database. When patients are discharged from hospital in Tayside, the code for their diagnoses (Office for Population Censuses and Surveys [OPCS4]) are entered on the Tayside section of the SMR1 database, with the CHN as an identifier. Details of all admissions since 1980 are held within MEMO. The CHN allows the temporal linking of diabetes-specific data with admissions. A case was defined as any patient who underwent any LEA in a Tayside hospital during the period 1 January 1992 to 31 December 1995. A minor amputation was defined as any LEA distal to the ankle joint (OPCS4 codes X11.1, X11.2, X11.8, and X11.9); a major amputation was any LEA through or proximal to the ankle joint (OPCS4 codes X09.2-5, X09.9, X10.1, X10.3-4, and X10.8-9). The use of the SMR1 database has been shown to be robust in Tayside for the identification of amputations (5).

The 10 years prior to 1 January 1992 was used as a screening period. Subjects who had a major LEA during this time were defined as prevalent cases and excluded from analysis. Patients who were not excluded and underwent any amputation after 1 January 1992 were followed-up for primary and secondary end points.

The primary end point was mortality after the first LEA. Secondary end points were the time to a major event requiring hospital admission after the incident LEA. Major events were defined by the ICD-9 or OPCS4 code. Patients were not censored after the first event. Major events were defined as acute coronary syndrome (ICD-9 codes 410 and 411), angina (ICD-9 code 413), congestive cardiac failure (ICD-9 codes 428.0, 428.1, 428.9, and 518.4), PVD (ICD-9 codes 443 and 250.7), stroke (ICD-9 codes 435 and 436), and major amputation (OPSC4 codes X09.2-5, X10.1, X10.4, and X10.8-9).

This group does not include reamputation of a nonhealing stump or recurrent amputation after a previously healed amputation. Those who underwent minor amputations as index cases were followed-up for major amputation of either limb. Those who underwent major amputation as the index procedure were followed-up for major amputation of the contralateral limb.

The cohort consisted of all subjects with incident LEA from 1 January 1992 to 31 December 1995. The end of follow-up for hospitalization was 31 March 1996. Follow-up for mortality was originally to 31 March 1998, but recently updated analysis has allowed us to follow the study population to 1 January 2005. Survival times were plotted using the Kaplan-Meier method and were calculated from the date of first LEA to death or end of study, whichever was earlier. Those subjects who died before 31 March 1998 were treated as censored for the hospital outcomes. The log-rank test was used to analyze the outcomes of mortality. Previous studies have shown the incidence of diabetes to be greater in more deprived groups (13). Analyses were therefore adjusted for the covariates of age at LEA, sex, and social deprivation.

Social deprivation was defined using the Carstairs score. This uses U.K. decennial census data to calculate a single score for each postcode area using the *Z*-score technique from information on employment, overcrowding, car ownership, and social class. Seven categories are defined ranging from the most affluent (class 1) to the most deprived (class 7). There were few subjects in class 7, and therefore, this was combined with class 6 (14).

For the secondary outcomes, logistical regression modeling was carried out with the reason for admission as a binary outcome to compare the proportions of patients with diabetes relative to nondiabetic individuals who were hospitalized for any of the major end points. All regression analyses were adjusted for age, sex, and social deprivation. This analysis used the patient as the unit of observation. All statistical analyses were carried out using SAS (version 6.12).

RESULTS — From the study population of 316,002 eligible residents, 10,616 were identified with diabetes (3.36%). We identified 403 major LEAs during the study period. Of these, 13 (8 with diabetes and 5 without) had previous major LEA and were excluded, leaving 390 major-incident LEAs during the study period. Of these, 119 (30.5%) had diabetes and 271 (69.5%) did not. This represents an incidence of 1.12% of all patients with diabetes over 3.33 years. Only three amputations were due to trauma (one diabetic patient and two nondiabetic patients). Age, sex, social deprivation,

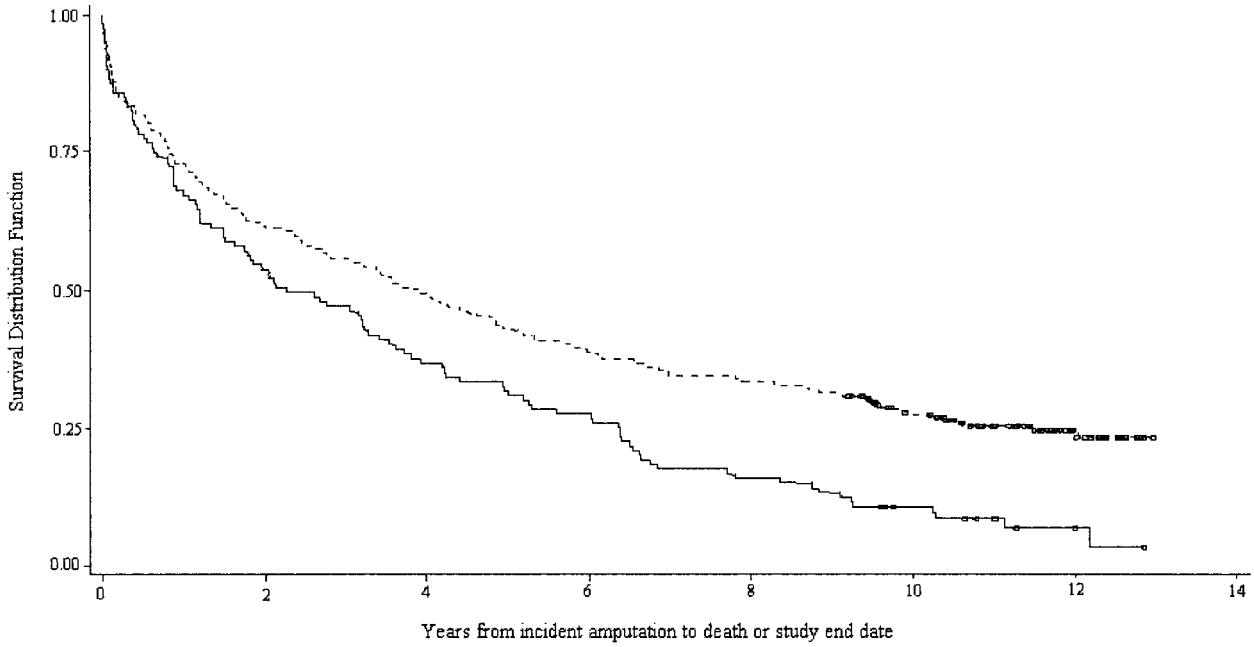

Figure 1—*Survival function by diabetes status. Diabetic patients are represented by the solid line; nondiabetic patients are represented by the dashed line.*

and diabetes status were recorded for each patient (Table 1). There were significantly more male than female patients, but results were adjusted for this potential bias. There was no difference in age between the groups. The cohort shows no trend in diabetes status by deprivation and no difference in the distribution of deprivation between those with and without diabetes.

In patients with diabetes, the median survival (50%) was 27.2 months compared with 46.7 months for nondiabetic patients (log-rank test $P = 0.0001$) (Fig. 1). From 4 years to the end of the study, there was a significant difference in mortality between those with and without diabetes (Table 2). Patients with diabetes who underwent incident amputation have a hazard ratio (HR) for mortality of 1.57 (95% CI 1.24–1.99) times that of a nondiabetic patient over 12 years follow-up and 1.58 (1.25–2.00) when adjusted for social deprivation. When adjusted for age and sex, the HR is 1.55 (1.22–1.98) times that of a nondiabetic patient. The HR remains at 1.55 (1.22–1.98) times that of a nondiabetic patient when results are adjusted for age, sex, and social deprivation.

The median length of time from discharge to admission with PVD is longer in patients with diabetes than those without (165 vs. 47 days, respectively, Wilcoxon $P = 0.03$). Otherwise, there is no significant difference between the groups for time to hospitalization for the other major end points (Table 3). The Cox proportional HRs for the incidence of hospitalization for each of the other major end points are given (Table 3). The major end points are given in terms of HRs adjusted for age, sex, and social deprivation. The adjusted HRs for congestive cardiac failure and further major amputations are significant. The risk of hospitalization with congestive cardiac failure in patients with diabetes is over twice that of a nondiabetic subject (Table 3).

CONCLUSIONS — This study shows an increased risk of death after incident amputation in patients with diabetes compared with the nondiabetic population. Patients with foot ulcers have an approximate twofold risk of death even without amputation (15). There is also increased morbidity, as assessed by admission to the hospital for further amputation and cardiac failure.

Ischemia is a contributory, if not the major, factor determining the need for major LEA (9,16). Patients with diabetes undergoing amputation have a higher subsequent death rate than those without, suggesting that vascular disease in diabetes is more severe or other factors are contributing to the increased mortality. We demonstrate that cardiac failure is more prevalent. It is known that after equivalent myocardial infarction, patients with diabetes are more likely to develop cardiac failure (17), and it is likely to be more

Table 2—*Survival rates after amputation according to diabetes status*

Year(s) after amputation	Nondiabetic patients	Diabetic patients	*P* value*
n	271	119	
1	197 (72.7)	80 (67.2)	NS
2	167 (61.6)	64 (53.8)	NS
3	151 (55.7)	56 (47.1)	NS
4	134 (49.4)	44 (37.0)	0.02
5	116 (42.8)	38 (31.9)	0.04
7	96 (35.4)	21 (17.6)	0.0004
10	62 (22.9)	10 (8.4)	0.0007
12	20 (7.4)	3 (2.5)	0.06

Data are *n* (%). *By χ^2 test.

Table 3—*Cox proportional hazards model comparing diabetic and nondiabetic subjects requiring hospitalization with major end points, whether incident or prevalent*

End point	Diabetes (yes/no)	Adjusted for social deprivation	Adjusted for age and sex	Adjusted for age, sex, and social deprivation
ACS	1.729 (0.801–3.734)	1.753 (0.811–3.789)	1.862 (0.839–4.133)	1.925 (0.867–4.271)
Angina	2.236 (0.907–5.509)	2.279 (0.923–5.667)	1.875 (0.743–4.730)	1.907 (0.743–4.893)
CCF	2.489 (1.262–4.910)	2.488 (1.262–4.906)	2.255 (1.123–4.530)	2.261 (1.120–4.566)
PVD	1.258 (0.916–1.727)	1.266 (0.922–1.740)	1.140 (0.822–1.579)	1.160 (0.836–1.609)
Stroke	1.743 (0.860–3.534)	1.733 (0.855–3.516)	1.369 (0.667–2.809)	1.358 (0.660–2.797)
Further major amputation	2.202 (1.310–3.702)	2.208 (1.312–3.715)	1.943 (1.139–3.316)	1.945 (1.135–3.332)

Data are provided unadjusted and adjusted for age, sex, and social deprivation (95% CIs). ACS, acute coronary syndrome; CCF, congestive cardiac failure.

severe (18,19) than in patients without diabetes.

Half of all nontraumatic LEAs are performed in patients with diabetes (20). Amputation alone is a predictor of poor outcome in patients with a perioperative 30-day mortality of between 8 and 23% (21–25). Recent evidence suggests that the more proximal the amputation, the greater the risk of perioperative death, possibly reflecting more severe vascular disease. Subramaniam et al. (24) showed the 30-day mortality for above-knee versus below-knee amputations to be 17.5 and 4.2%, respectively, with a total perioperative mortality of 7.4%. Diabetes status per se was not associated with death at this stage. Only at 10 years postamputation was there a significant difference in mortality between patients with and without diabetes. We demonstrate increased mortality in patients with diabetes at only 4 years post-LEA. This difference may be due to differences in the power of the two studies and ethnic differences between the two populations.

This study confirms what others have shown. Our survival rates postamputation in patients with diabetes are similar to other series at 1 year, being 67.2% (our data) and 69.4% (25) and, at 5 years, 31.9% (our data) and 30.9% (25). The figures for nondiabetic patients were also similar between the two studies. The Strong Heart Study showed a survival rate of 23.9% at 8 years postamputation in patients with diabetes (26) compared with 8.4% at 10 years in our study.

Within 1 year of the incident amputation, between 9 and 13% of patients with diabetes will undergo a further ipsilateral or contralateral amputation (27) and between 30 and 50% of patients will undergo a contralateral LEA between 1 and 3 years after the first (28). This compares with our study where 22% underwent additional amputation at a median of 219 days (~7 months). We demonstrate that further amputation is twice as likely in patients with diabetes. Therefore, secondary prevention of foot ulceration is as important as primary prevention. The prevention of diabetic foot ulceration involves the relief of pressure, ischemia, infection, and regular foot care.

We have shown that time to hospitalization with further PVD is longer in patients with diabetes than those without. LEA in patients without diabetes is almost exclusively performed as a result of PVD. A significant number of amputations in patients with diabetes occur secondary to infection in a neuropathic foot, with adequate blood supply, possibly accounting for this difference.

Patients with PVD often have generalized vascular disease, being six times more likely to die from cardiovascular causes over a 10-year period than those without (29). This study shows that the risk of developing congestive cardiac failure following amputation in the presence of diabetes is twice that of those who are nondiabetic. Although not all amputations are due to PVD, in the majority, it contributes to the need for amputation and these patients should receive aggressive treatment for cardiovascular risk factors. Recent studies have shown that the addition of ACE inhibitors for patients with peripheral arterial disease yielded a 25% risk reduction in cardiovascular events, with a number needed to treat of only 18 (30). Similar evidence is available for the use of antiplatelet drugs and hydroxymethylglutaryl-CoA inhibitors in those with PVD (31–35).

All patients undergoing amputation have a high mortality rate. It is even higher in patients who have preexisting diabetes. Preexisting diabetes puts patients at increased risk of further amputation and cardiac failure, highlighting the need for a more aggressive approach to the management of cardiovascular risk factors in those who undergo amputation and have diabetes.

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