

Time-Dependent Impact of Diabetes on Mortality in Patients After Major Lower Extremity Amputation

Survival in a population-based 5-year cohort in Germany

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OBJECTIVE—To estimate the impact of diabetes on mortality in patients after first major lower extremity amputation (LEA).

RESEARCH DESIGN AND METHODS—Using claims data of a nationwide statutory health insurance, we assessed all deaths in a cohort of all 444 patients with a first major LEA since 2005 (71.8% male; mean age 69.1 years; 58.3% diabetic; 43% with amputation above the knee) up to 2009. Using Cox regression, we estimated the time-dependent hazard ratios to compare patients with and without diabetes.

RESULTS—The cumulative 5-year mortality was 68% in diabetic and 59% in nondiabetic individuals. In the first course, mortality was lower in diabetic compared with nondiabetic patients. Later, the diabetes risk increased yielding crossed survival curves after 2 to 3 years (time dependency of diabetes; $P = 0.003$). Age- and sex-adjusted hazard ratios for diabetes were as follows: 0–30 days: 0.50 [95% CI 0.31–0.84]; 31–60 days: 0.60 [0.25–1.41]; 61 days to 6 months: 0.75 [0.38–1.48]; >6–12 months: 1.27 [0.63–2.53]; >12–24 months: 1.65 [0.88–3.08]; >24–36 months: 2.02 [0.80–5.09]; and >36–60 months: 1.91 [0.70–5.21]. The pattern was similar in both sexes. In the full model, significant risk factors for mortality were age (1.05; 1.03–1.06), amputation above the knee (1.50; 1.16–1.94), and quartile category 3 or 4 of the number of prescribed medications (1.64; 1.12–2.40 and 1.76; 1.20–2.59). Further adjustment for comorbidity did not alter the results.

CONCLUSIONS—In this population-based study, we found a time-dependent mortality risk of diabetes following first major LEA, which may be in part a result of a healthier lifestyle in diabetic patients or the access to specific treatment structures in diabetic individuals.

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Lower extremity complications, particularly ulceration and amputation, are significant sources of morbidity in the diabetic population. Although the reduction of lower extremity amputation (LEA) in diabetes has frequently been cited as a primary objective by health systems and organizations (1,2), diabetic

individuals still have a largely increased LEA risk compared with nondiabetic patients (3,4). Avoidance of amputation should not only be targeted because of the associated economic consequences (high costs because of repeated hospitalizations, rehabilitation, home care, and social-service support) but also because

of quality-of-life issues. Alternative treatment options might seem costly in the short term, but most cost-effectiveness analyses that also considered the long-term perspective have concluded that treatment alternatives in which the limb is saved are most cost effective (see Supplementary Ref. 1). Furthermore, diabetes has been considered to be associated with an excess mortality in patients after LEA, in particular in the perioperative period and during the first year (5,6). Some studies found contrasting results, with similar or reduced mortality in diabetic compared with nondiabetic patients (7–11; and Supplementary Refs. 2–4). However, several studies are not population based but use data from specialized diabetes centers or had short follow-up periods. Thus results remain controversial.

Hence, the aim of our study was to evaluate the mortality risk in diabetic and nondiabetic individuals after a first major LEA since 2005 up to 2009 in Germany, using claim data of a nationwide statutory health insurance.

RESEARCH DESIGN AND METHODS

Study population and data assessment

We used data of a cohort of patients with incident LEA, for which analyses on incidence have been published elsewhere (3). In brief, these patients were derived from the Gmünder ErsatzKasse (GEK), a statutory health insurance company that insured 1.6 million people located in all regions of Germany (1.9% of the German population). We included all people who were members of the GEK for at least 1 year within the period 1 January 2004 to 31 December 2007. Diabetic patients were defined according to an established procedure (12) as subjects with at least one of the following characteristics: 1) diabetes diagnosis (ICD E10–E14) in at least three of four consecutive quarters, 2) at least two prescriptions of antidiabetic

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medication (ATC code A10) within 12 months, or 3) at least one prescription of an antidiabetic medication and one diabetes diagnosis or one measurement of blood glucose or HbA_{1c} within 12 months. We assessed all incident LEAs between 2005 and 2007 in patients with an amputation-free period of at least 1 year. Lower limb amputations were classified according to a previous study (3) using specific operation procedure codes (OPS codes 5–864.X, 5–865.X, and 5–869.0) of the hospital discharge documentation. A total of 994 patients with a first minor or major LEA were included.

The current study was restricted to major amputations (any resection proximal to the midtarsal level, according to the 2007 International Consensus of the Diabetic Foot [13]). Patients with minor amputations were further followed up until 31 December 2009 and were included if a major amputation occurred. A total of 454 patients with an incident major LEA were studied, of whom 418 had their event between 2005 and 2007. The index date was the day of the first major amputation. We further excluded all people coinsured as a dependent and members who left the GEK for reasons other than death within the study period ($n = 10$). Both criteria were applied to avoid informative censoring in the survival analysis (e.g., an insurance period ends because of death but this reason might not be documented in these cases). Our final cohort, therefore, comprised 444 patients with a first major LEA between 2005 and follow up to 2009.

We further used medication claims data for the year preceding the index date. Treatment with cardiovascular drugs (β -blockers, ACE inhibitors, sartans, statins, ezetimibe, fibrates, and clopidogrel) and antidiabetic drugs (insulin, oral antidiabetic agents) was assessed. Because it has been shown that the number of distinct medications prescribed in the previous year is a good predictor of mortality (14), we included this indicator as a comorbidity measure. Furthermore, we assessed the following outpatient diagnoses: 1) hypertension (ICD-10: I10–I15), 2) chronic ischemic heart diseases (ICD-10: I20–I21, I25), 3) cerebral ischemia/chronic stroke (ICD-10: G45, I60–I64, I69), and 4) renal failure (ICD-10: N18–N19) coded according to a previous study using German claims data (see Supplementary Ref. 5). At least one of these diagnoses had to be recorded in a 1-year period (including the quarter of

the index date and the preceding three quarters). Quarters had to be chosen because this is the basic time period for coding diagnoses in outpatient care in Germany.

Statistical analysis

Target variable was the time from the first major LEA up to death or the end of the study period (31 December 2009), whichever came first. We assessed survival with the Kaplan Meier estimator, stratified for diabetes. Crude differences between diabetic and nondiabetic individuals were planned to be statistically compared using the log-rank test, if the proportional hazard assumption was not violated. But because survival curves of the diabetic and the nondiabetic group were crossing, proportional hazards could not be assumed, which was statistically tested using the test proposed by Grambsch and Therneau (15). We then performed Cox regression using discrete time intervals to model the time dependency of diabetes (16) and to evaluate predictors of death in multivariate analyses. As predictors, we included diabetes, interaction of diabetes with the discrete time intervals (30 and 60 days, 6, 12, 24, 36, and 60 months), and age (as continuous variable). In a second model, the location of the amputation (below or above knee) and the number of prescribed medications, which were categorized into quartiles, were added as further independent variables. In a sensitivity analysis, we also included the above given outpatient diagnoses for hypertension, chronic ischemic heart diseases, cerebral ischemia/chronic stroke, and renal failure.

The Cox regression was also performed stratified for men and women.

All analyses were performed using R (A Language and Environment for Statistical Computing, Release 2.10.1; R Foundation for Statistical Computing, <http://www.R-project.org>), and the results of the Cox models were verified using the Statistical Analysis Systems SAS (SAS for Windows XP Professional, Release 9.2 TS2M0; SAS Institute, Cary, NC).

RESULTS—Results did not differ substantially between men and women. Thus we report the results for the whole population.

Baseline characteristics of the study population

Of the 444 individuals with incident major amputation between 2005 and up

to 2009, 319 (71.8%) were male, and mean age (SD) was 69.1 (11.7) years. Of the individuals, 259 (58.3%) of them had diabetes and 192 (43.2%) of the LEAs were above the knee. Diabetic patients were slightly older, more likely to be male, and had more prescribed medications compared with nondiabetic individuals. The proportion of amputations above the knee was lower in diabetic than in nondiabetic patients. Diabetic patients were more likely to have a diagnosis of hypertension, chronic ischemic heart diseases, cerebral ischemia/chronic stroke, or renal failure. Table 1 shows the description of the subjects with incident major amputation, stratified for diabetes.

Survival and mortality in the study population

Overall, 245 individuals died within the study period of up to 5 years, 146 and 99 with and without diabetes, respectively. The mean observation time per patient (SD) was 1.9 (1.6) years.

Figure 1 shows the Kaplan-Meier curves crossing each other after about 2 years in the whole population (number of survivors under the curves in Table 2). The assumption of proportional hazards seemed to be violated: there was a significant time dependency of diabetes ($P = 0.003$). This means corresponding to the figure that the relative mortality risk as a result of diabetes was time dependent: in the first time after LEA, diabetic individuals had better survival. But in the time course the diabetes risk increased yielding crossed survival curves after about 2 to 3 years. The relative mortality risk for diabetes, adjusted for sex and age, was as follows: baseline 0–30 days: 0.50 [95% CI 0.31–0.84]; 31–60 days: 0.60 [0.25–1.41]; 61 days to 6 months: 0.75 [0.38–1.48]; >6 to 12 months: 1.27 [0.63–2.53]; >12 to 24 months: 1.65 [0.88–3.08]; >24 to 36 months: 2.02 [0.80–5.09]; and >36 to 60 months: 1.91 [0.70–5.21]. As expected, age was significantly associated with mortality. Cumulative mortality after 1 month, 1 year, and 5 years, as derived from the Kaplan-Meier estimates, was 10, 31, and 68% in diabetic and 19, 40, and 59% in nondiabetic individuals, respectively.

Model 2 in Table 3 shows the results when the LEA location and the number of prescribed medications are included as further predictors. The hazard ratios of model 1 remained. Amputation above the knee (1.50; 1.16–1.94), and quartile category 3 or 4 of number of prescribed

Table 1—Description of the study population: patients with first LEA during 2005 to 2009 (GEK insureds, Germany)

	Diabetes	No diabetes	All
n	259	185	444
Mean age (years) (SD) ¹	69.3 (10.7)	68.8 (13.1)	69.1 (11.7)
Sex (% male)	75.7	66.5	71.8
Above-knee amputation (%)	37.5	51.4	43.2
Number of prescribed medications ²			
First quartile	11	6	8
Median	16	11	14
Third quartile	21	16	19
Maximum	47	37	47
Insulin therapy (%)	62.5	—	36.5
Oral antidiabetic medication (%) ²	38.6	—	22.5
Cardiovascular medication (%) ^{2,3}	87.3	63.8	77.5
Diagnoses in outpatient care ⁴			
Hypertension (%)	79.2	62.7	72.3
Chronic ischemic heart diseases (%)	46.7	32.4	40.8
Cerebral ischemia/chronic stroke (%)	25.9	20.5	23.6
Renal failure	31.7	13.5	24.1

¹Age at time of first major LEA; ²substances, in the year before first major LEA; ³β-blockers, ACE inhibitors, sartans, statins, ezetimibe, fibrates, and clopidogrel; ⁴in the quarter of the first major LEA and in the preceding 3 quarters (e.g., 1 year).

medications (1.64; 1.12–2.40 and 1.76; 1.20–2.59) were both significantly associated with mortality.

The inclusion of hypertension, chronic ischemic heart diseases, cerebral

ischemia/chronic stroke, and renal failure in a sensitivity analysis did not alter our findings (data not shown). Furthermore, none of these variables were statistically significant or associated with mortality.

CONCLUSIONS

Study findings and implications

In this population-based study we could analyze survival in patients with incident major amputation in Germany up to 5 years (2005–2009), with a focus on diabetes as a predictor. As expected, we found a high mortality in this population. After 3 years follow-up, more than 50% of the patients in our cohort had died. Interestingly, the influence of diabetes in our study was significantly time dependent: in the first time after incident LEA, mortality was lower in diabetic than in nondiabetic individuals. There was an increasing trend of diabetes risk during observation time, and after about 2 to 3 years, diabetic individuals had a higher mortality than nondiabetic individuals. The number of prescribed medications, included as a proxy for comorbidity, and the amputation level were significantly associated with mortality; however, they did not alter these estimates. Looking for an explanation of our finding, one could argue that diabetic individuals have more comorbidities, as indicated by medications and outpatient diagnoses, but are, however, more closely monitored by several specialists because of their chronic disease, and if problems arise they are identified and treated early. In Germany, nationwide disease management programs for diabetes have been implemented since 2003. These programs defined contents and time frames for the treatment of diabetes and its complications, and they provided interfaces among the different levels of care. Diabetic individuals were more likely to have an amputation below the knee eventually because of the more distally pronounced distribution pattern of peripheral arterial disease compared with nondiabetic patients (17,18). In previously published series, patients with below-knee amputation had been reported to have significantly better survival outcomes than above-knee amputees (7,19,20). When we stratified our analyses for amputation level, the time dependency of diabetes seemed to be only present for below-knee amputations, not for amputations above the knee (data not shown). However, the case numbers were too low to yield valid estimates. Further analyses are warranted. In the above-mentioned disease management programs, networks of specialized physicians have been introduced in various German regions and are thought to be responsible for a recently

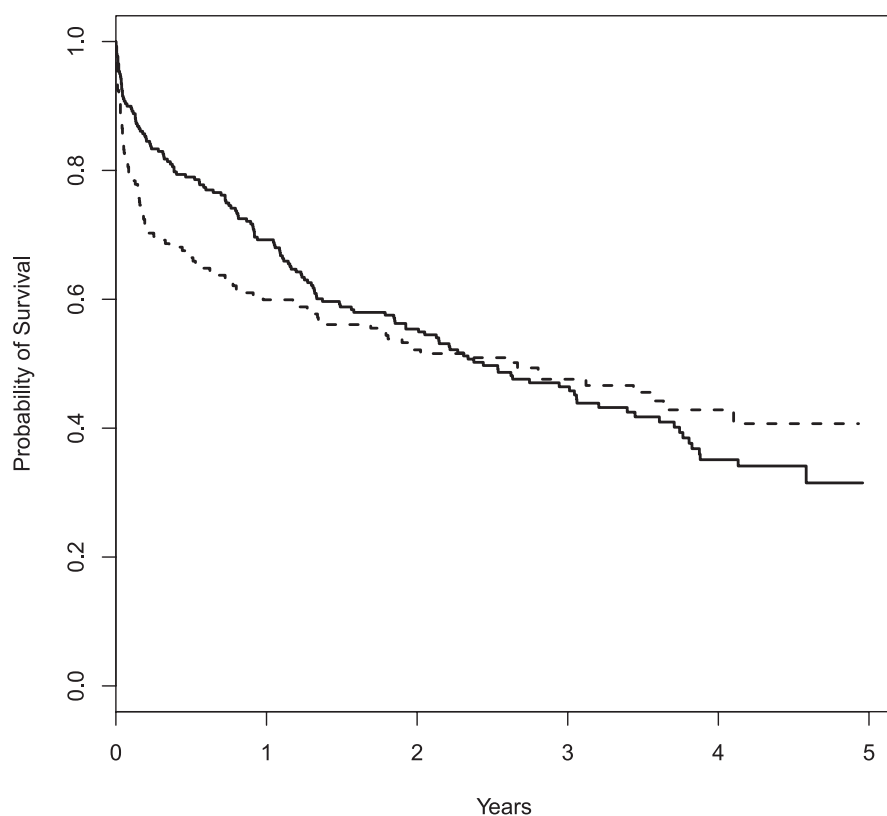


Figure 1—Crude survival curves after first major LEA (GEK insureds, Germany, 2005–2009).

Table 2—Survival after first major LEA (GEK insurants, Germany, 2005–2009)

Survivors	Time					
	1 Month	1 Year	2 Years	3 Years	4 Years	5 Years
No diabetes	81 (75–86)	60 (53–67)	52 (45–60)	48 (41–56)	43 (35–52)	41 (33–50)
Diabetes	90 (86–93)	69 (64–75)	55 (50–62)	46 (40–53)	35 (29–43)	32 (24–41)

Data are % (95% CI).

observed decline in major amputation rates as well as reductions of the excess amputation risk because of diabetes in German diabetic populations (3,21). One might argue that even those diabetic patients in whom major amputation cannot be avoided might profit from improved treatment structures by achieving more distal major amputation levels, tighter glycemic control, and more aggressive cardiovascular risk management. Such a concept has been proven to be effective by improving 5-year survival rates in diabetic foot ulcer patients recently (22). In this context the observed larger number of prescribed medications in diabetic patients also might be a hint for more aggressive management of cardiovascular risk factors, not only a marker of comorbidity.

Other factors may play a role, like a lower proportion of smokers among diabetic individuals undergoing amputation compared with their nondiabetic counterparts (see Supplementary Ref. 2). However, in our data we have no information about detailed clinical or lifestyle

variables, e.g., smoking habits or glycemic control, and only limited information about history of coronary or cerebrovascular events, chronic heart failure, and renal function. Exact causes of death also cannot be determined by our data.

Comparison with other studies

The 1-year mortality of diabetic patients in our study (31%) was comparable with the numbers from other studies (31–34%) (7,11,23). The 5-year mortality in diabetic patients in our cohort showed conformity with those from the study of Aulivola et al. (7) (68 and 69%, respectively) but was lower than reported from other cohorts investigated in the 1990s reporting 80–90% mortality after 5 years (5,10). Mortality reported from nondiabetic patients in other studies showed much more variability, probably because of more heterogenous patient cohorts (1-year: 29–43%, 5-years: 49–77%) (5,7,8,10,11,23).

Several studies evaluated mortality after incident amputations in diabetic compared with nondiabetic patients.

Diabetes has been considered to be associated with an excess mortality in patients after LEA, in particular in the perioperative period and during the first year (5,6). Some studies found contrasting results, with similar mortality in diabetic compared with nondiabetic patients (7–11,23; and Supplementary Refs. 2–4). However, several studies were not population based but used data from specialized diabetes centers. Only a few studies looked over a 5-year period. An improved survival of diabetic patients 1 and 2 years after major amputation compared with nondiabetic patients and a loss of this difference during longer follow-up periods has been described also by Pohjolainen and Alaranta (10). A few other studies found similar early death rates (up to 3 years) for diabetic and nondiabetic patients following major amputation with worsening of the prognosis for diabetic patients during further observation (up to 10 years) (7–9). Most other studies did not evaluate an interaction between diabetes and time (5,6,9,23). Thus study results remain conflicting, and further studies are warranted to confirm and explain our findings.

Study limitations and strengths

Several limitations have to be considered. First, in particular in the last years of observation, the case numbers are low, leading to a lack of power to detect statistically significant differences between patients with and without diabetes. Second, we have only limited information about clinical variables and do not know patients' lifestyles. However, we included the number of prescribed drugs as well as outpatient diagnoses of relevant comorbidities. We also had no information about the reason of amputation and thus could not exclude traumatic amputations. However, the proportion of amputations as a result of trauma can be considered to be low (see Supplementary Ref. 6). Finally, the insurants of the GEK are not representative for the German population with respect to age, sex, and socioeconomic position (24), which might have an impact on morbidity and on the utilization of health care resources. Thus a translation of our results in other populations should be performed with caution. However, the incidence of LEA in our population was well in line with the incidence of LEA in a study based on hospital records in a German region as was the proportion of patients with diabetes (21).

Table 3—Predictors for mortality after first major LEA, Cox regression (GEK insurants, Germany, 2005–2009)

	HR for death (95% CI)	
	Model 1	Model 2
Diabetes		
×0–30 days	0.50 (0.30–0.84)*	0.44 (0.26–0.74)*
×30–60 days	0.60 (0.25–1.41)	0.52 (0.22–1.23)
×60 days to 6 months	0.75 (0.38–1.48)	0.65 (0.32–1.29)
×6 to 12 months	1.27 (0.63–2.53)	1.11 (0.55–2.32)
×12 to 24 months	1.65 (0.88–3.08)	1.46 (0.78–2.76)
×24 to 36 months	2.02 (0.80–5.09)	1.76 (0.69–4.46)
×36 to 60 months	1.91 (0.70–5.21)	1.64 (0.60–4.49)
Age (years) (continuously, per year)	1.05 (1.04–1.07)*	1.05 (1.04–1.06)*
Sex (men vs. women)	1.01 (0.77–1.34)	0.98 (0.74–1.29)
Location of amputation (above vs. below knee)	—	1.50 (1.12–2.40)*
Quartile category of number of prescribed medications (baseline: quartile 1 [0–8])		
2 [8–14]	—	1.16 (0.79–1.70)*
3 [14–19]	—	1.64 (1.12–2.40)*
4 [19–47]	—	1.76 (1.20–2.59)

* $P < 0.05$.

The main strength of our study is that we were able to analyze a large population-based dataset without selection with respect to diabetes complications and that diabetes status could directly be assessed at study entry.

In conclusion, in our German population-based study, we found a high mortality in patients with a first major amputation. Interestingly, the influence of diabetes was time dependent: in the first ~2 to 3 years after first LEA, mortality was lower in diabetic than in nondiabetic individuals. Only thereafter, diabetic patients had a higher mortality than nondiabetic patients. Our observation is in contrast with several, but not all, studies. Possible explanations may be differences in comorbidities, the access to specific treatment structures for diabetic patients, or smoking habits, as indicated by a higher proportion of above-knee amputations in nondiabetic patients. However, results remain conflicting, and further studies are warranted to confirm and explain the results.

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A.I. initiated the study, developed the study protocol, wrote the manuscript, and is the guarantor for the article. M.S. coordinated data analysis and performed the statistical analysis. S.M. provided clinical expertise. J.G. developed the study protocol. B.H. and G.Gi. gave statistical expertise. G.Gl. coordinated data analysis. F.H. developed the study protocol and coordinated data analysis. All authors commented on manuscript drafts.

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