Time-Dependent Impact of Diabetes on Mortality in Patients With Stroke

Survival up to 5 years in a health insurance population cohort in Germany

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OBJECTIVE—To estimate the impact of diabetes on mortality in patients after first stroke event.

RESEARCH DESIGN AND METHODS—Using claims data from a nationwide statutory health insurance fund (Gmünder ErsatzKasse), we assessed all deaths in a cohort of 5,757 patients with a first stroke between 2005 and 2007 (69.3% male, mean age 68.1 years, 32.2% with diabetes) up to 2009. By use of Cox regression, we estimated time-dependent hazard ratios (HRs) to compare patients with and without diabetes stratified by sex.

RESULTS—The cumulative 5-year mortality was 40.0 and 54.2% in diabetic men and women, and 32.3 and 38.1% in their nondiabetic counterparts, respectively. In males, mortality was significantly lower in diabetic compared with nondiabetic patients in the first 30 days (multiple-adjusted HR 0.67 [95% CI 0.53–0.84]). After approximately a quarter of a year, the diabetes risk increased, yielding crossed survival curves. Later on, mortality risk tended to be similar in diabetic and nondiabetic men (1–2 years: 1.42 [1.09–1.85]; 3–5 years: 1.00 [0.67–1.41]; time dependency of diabetes, $P = 0.008$). In women, the pattern was similar; however, time dependency was not statistically significant ($P = 0.89$). Increasing age, hemorrhagic stroke, renal failure (only in men), levels of care dependency, and number of prescribed medications were significantly associated with mortality.

CONCLUSIONS—We found a time-dependent mortality risk of diabetes after first stroke in men. Possible explanations may be type of stroke or earlier and more intensive treatment of risk factors in diabetic patients.

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Cardiovascular events, such as strokes, are significant sources of morbidity in the diabetic population. Although the reduction of stroke in diabetes has frequently been cited as a primary objective by health systems and organizations (1), diabetic individuals still have an approximately twofold stroke risk compared with nondiabetic patients (2–6). Avoidance of stroke should be targeted for both the associated economic consequences (high costs due to repeated hospitalizations, rehabilitation, home care, and social service support) and quality-of-life issues.

Diabetes has been considered a risk factor for higher mortality in patients after stroke (7–9). However, to the best of our knowledge, there are only a few population- or insurance-based studies that investigate mortality after stroke in the diabetic population compared with the nondiabetic population (10–12), and these studies analyze only single subtypes of stroke or shorter periods of follow-up.

The studies find a higher mortality in the diabetic population for the 28-day fatality as well as for periods up to 1 year. The latter finding is in contrast to the short-term mortality after beginning renal replacement therapy and after amputation, where a time-dependent impact of diabetes for mortality has been found, with lower or virtually the same mortality in diabetic patients during the first period (13–15). However, thereafter, diabetes became a risk factor. For mortality after beginning renal replacement therapy, differences between men and women have been observed (13–15).

Hence, the aim of our study was to evaluate the mortality risk in diabetic and nondiabetic individuals after a first stroke up to 5 years of follow-up in Germany, using claims data from a nationwide statutory health insurance fund. We further focused on differences between men and women.

RESEARCH DESIGN AND METHODS

Database and identification of patients

We used data of a cohort of patients with incident stroke, for which analyses on incidence and attributable risks have been published elsewhere (2). In brief, these patients were derived from a statutory health insurance company, the Gmünder ErsatzKasse (GEK), which insures ~1.6 million people located in all regions of Germany (1.9% of the German population). We included only first strokes between 2005 and 2007 in persons with a period free from stroke of at least 1 year. Strokes (cerebral ischemia, intracerebral hemorrhage, subarachnoid hemorrhage, and stroke of uncertain cause, but no transient ischemic attacks) were defined following the World Health Organization definition (16), using specific ICD-10 codes of hospital admissions (I60–I61, I63–I64, and including I62 to avoid missing unspecific cases). Diabetes status was assessed according to an established algorithm that has been used in several

studies analyzing claims data of German statutory health insurance funds (13,17). A person was identified as having diabetes if at least one of the following characteristics was fulfilled within 12 months in the observation period between 2004 and 2007: *1*) diabetes diagnosis (ICD E10–E14) in at least three of four consecutive quarters in outpatient care, *2*) at least two prescriptions of antihyperglycemic medication (Anatomical Therapeutic Chemical code A10) within 12 months, or *3*) at least one prescription of an antihyperglycemic medication and one diabetes diagnosis or one measurement of blood glucose or HbA$_{1c}$ within 12 months.

In the previously published analysis, data of 6,160 patients (*n* = 1,932 had diabetes) with an incident stroke between 2005 and 2007 were available. For this study, only persons aged ≥30 years were included (*n* = 6,100). We further excluded all persons coinsured as a dependent and members who left the GEK for reasons other than death within the study period (*n* = 343). 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, consisted of 5,757 patients with a first stroke during 2005 to 2007 and follow-up until the end of 2009.

Covariates

From the claims data, we assessed reimbursed medications as well as services of the long-term care insurance for the year preceding the index event (the first stroke). Treatment with cardiovascular drugs (β-blockers, ACE inhibitors/sartans, and calcium antagonists) and antihyperglycemic drugs (insulin and oral antihyperglycemic agents) was assessed. We determined the number of distinct medications prescribed within this period as a comorbidity measure because it has been shown to be a good predictor of mortality (18). Services from the German long-term care insurance are provided to those who require support in the activities of daily living, including personal hygiene, eating, mobility, and—separate from personal care—housekeeping. There are three levels of care dependency related to the estimated time required for assistance and indicating considerable (level 1), severe (level 2), and extreme (level 3) care dependency (19). The highest level of dependency within the year before the index date was included

as a proxy for functional and cognitive impairments.

Furthermore, we assessed the following outpatient diagnoses: hypertension (ICD-10: I10–I15), chronic ischemic heart diseases (ICD-10: I20–I21, I25), and renal failure (ICD-10: N18–N19) coded according to a previous study using German claims data (20). 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

The main analyses were performed stratified for men and women. The outcome of interest was the time from the first stroke up to death or the end of the study period (31 December 2009), whichever came first. We assessed crude survival with the Kaplan-Meier estimator, stratified for diabetes as well as for sex. The appropriateness of the Cox proportional hazards assumption was further visualized using log-log survival plots, that is, plotting log (-log(S(t)) against log(t). If the assumption is fulfilled, the curves should be parallel. Furthermore, we tested the proportional hazards assumption via the test proposed by Grambsch and Therneau (21). Because we expected that the interaction between diabetes and time was statistically significant, which means that the proportional hazards assumption was violated, we performed Cox regression using discrete time intervals to model the time dependency of diabetes (22). We estimated time-dependent hazard ratios (HRs) and 95% CIs in multivariate analyses. As predictors, we included diabetes, interaction of diabetes with the discrete time intervals (30 days and 6, 12, 24, 36, and 60 months), and age (as continuous variable). We chose the time intervals in line with previous studies to be able to compare our results and on the basis of clinical experience. In a second model, type of stroke (ischemic, hemorrhagic, and not specified), number of prescribed medications (as continuous variable), level of care dependency (four categories), and the above-stated outpatient diagnoses for hypertension, coronary heart diseases, and renal failure were added as further independent variables.

All analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC). The results of the Cox models were verified using R (A Language and Environment for Statistical Computing, Release 2.12.1,

R Foundation for Statistical Computing, http://www.*R*-project.org).

The study was conducted according to the principles expressed in the Declaration of Helsinki. We considered the STROBE statement (Strengthening the Reporting of Observational Studies in Epidemiology) and the criteria of a national good practice guideline (23,24). The use of health insurance claims data for scientific research is regulated by the German Code of Social Law (SGB X). Because our study was based on pseudonymous data, we did not have to obtain informed consent. According to the Good Practice of Secondary Data Analysis, a national guideline for the use of administrative databases, no approval of an ethical committee was required (24).

RESULTS

Baseline characteristics of the study population

Table 1 shows the characteristics of the 5,757 individuals with a first stroke between 2005 and 2007 in total as well as stratified for diabetes and sex. Cerebral infarction was by far the most common type of stroke, followed by cerebral hemorrhage and subarachnoid hemorrhage. Comorbidities, such as hypertension and coronary heart disease, were predominant among these individuals. Approximately 13% were at least considerable (level 1) care dependent. On average, 7.2 distinct medications were prescribed.

For both sexes, diabetic patients were older than nondiabetic individuals and had more ischemic strokes compared with nondiabetic patients. The latter was particularly true for women. Persons with diabetes were more likely to have a diagnosis of hypertension, coronary heart disease, or renal failure, with similar differences among men and women. They also had a higher level of care dependency, which was particularly pronounced in the female population. Likewise, diabetic patients had an almost twofold higher intake of drug prescriptions for both sexes, which was also true for cardiovascular medications, such as β-blockers, ACE inhibitors/sartans, and calcium antagonists.

The mean observation time was 2.66 years (25 and 75% quartiles 1.98 and 3.83, respectively). Overall, 1.828 individuals died within the study period of up to 5 years, including 470 and 698 men as well as 264 and 396 women with and without diabetes, respectively. The cumulative mortalities, including the population at risk, are presented in Table 2.

Table 1—*Description of the study population: GEK insurants with first incident stroke during 2005 to 2007, stratified for diabetes and sex*

		Diabetes		No diabetes	
	Total (n = 5,757)	Men (n = 1,304)	Women (n = 550)	Men (n = 2,683)	Women (n = 1,220)
Age (years), mean (SD)*	68.1 (13.0)	69.9 (9.8)	76.3 (10.0)	65.3 (12.8)	68.6 (15.5)
Age (years), median (Q1–Q3)*	69.0 (60.0–78.0)	70.0 (64.0–77.0)	78.0 (70.0–83.0)	66.0 (56.0–75.0)	71.0 (57.0–81.0)
Subtype of stroke (%)					
Cerebral infarction	73.7	79.8	79.6	72.5	67.1
Hemorrhage	17.9	12.7	9.8	20.1	22.0
Cerebral	13.6	12.0	8.9	15.7	12.8
Subarachnoid	4.2	0.7	0.9	4.4	9.2
Other/unknown	8.4	7.4	10.6	7.4	10.9
Comorbidities (%)					
Hypertension	71.2	82.8	84.7	65.2	65.9
Coronary heart disease	28.5	40.7	36.4	24.5	20.7
Renal failure	9.4	14.4	15.1	7.4	5.8
Level of care dependency (%)**					
0	87.2	86.5	69.1	92.7	83.9
1	5.8	6.2	13.1	3.5	7.3
2	5.3	5.4	12.7	2.8	7.2
3	1.7	1.8	5.1	1.0	1.6
Prescribed medications, mean (SD)	7.2 (5.8)	9.2 (5.9)	11.3 (6.5)	5.4 (4.8)	7.2 (5.5)
Median number of prescribed medications (Q1–Q3)	6.0 (3.0–10.0)	8.0 (5.0–12.0)	10.0 (7.0–15.0)	4.0 (2.0–8.0)	6.0 (3.0–10.0)
Intake of specified medications (%)					
β-Blockers	40.2	48.3	57.1	33.9	38.0
ACE inhibitors/sartans	47.1	64.0	68.7	37.9	39.3
Calcium antagonists	22.9	30.4	35.1	17.6	20.9
Insulin	9.5	28.6	32.0	0.0	0.0
Oral antidiabetic drugs	14.2	43.3	45.8	0.0	0.0

*Age at time of incident stroke. **0 = none; 1 = considerable; 2 = severe; and 3 = extreme.

Impact of diabetes on survival and mortality

Figure 1 shows the Kaplan-Meier curves and the log-log survival plots. We present both since in the log-log plots, the early period after stroke event can be seen, whereas the Kaplan-Meier curves give a better picture of the later period. In men, the crude relative mortality risk as a result of diabetes was significantly time dependent ($P = 0.002$): in the first month after stroke, diabetic individuals had better survival, but thereafter, mortality risk in diabetic men increased, resulting in a higher survival in nondiabetic men. The curves cross each other after approximately a quarter of a year. After ~3 years, the curves seem to become more convergent again, which means that the difference between diabetic and nondiabetic men is no longer visible. A significant time dependency of diabetes on mortality could also be seen in multivariate analysis ($P = 0.008$). Adjusted for age, it yields a significant decreased mortality risk in diabetes within the first month

and an increased mortality risk in diabetes between 1 month and 3 years of follow-up, which was no longer the case after 3 to 5 years (model 1, Table 3). After further adjustment for comorbidities, level of care dependency, number of prescribed medications, and subtype of stroke, relative risks decreased somewhat but remained significantly increased between 1 and 3 years (model 2, Table 3).

In women, there is a quite similar pattern. However, time dependency was not statistically significant in crude ($P = 0.08$) or multivariate analysis ($P = 0.89$). The curves do cross, albeit only slightly, in the first week of follow-up, and the Cox model shows no significant decreased HR in the first months after stroke. Nevertheless, the relative risk of mortality in the fully adjusted model was significantly increased for diabetic women between 6 months and 1 year as well as between 2 and 3 years, with an almost twofold increased risk of diabetic women for the first time interval. Again, we found no significant differences between 3 and 5 years of follow-up.

Increasing age, renal failure (only in men), levels of care dependency, number of prescribed medications, and hemorrhage stroke were positively associated with mortality in the fully adjusted model (model 2, Table 3). In contrast, mortality was significantly lower in patients with a diagnosis of hypertension for both sexes.

CONCLUSIONS

Study findings and implications

In this study based on data of a nationwide health insurance fund, we analyzed survival in patients with incident stroke in Germany during a period of 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 5 years of follow-up, more than one-third of the patients in our cohort had died. It is interesting that the influence of diabetes in our study was significantly time dependent in men: in the first 30 days after incident stroke, mortality was lower in diabetic than in nondiabetic individuals.

Table 2—*Crude mortality estimates after first incident stroke: GEK insurants during 2005–2007, stratified for sex and diabetes*

	Time					
	1 month	6 months	1 year	2 years	3 years	5 years
Male						
No diabetes						
Number at risk	2,431	2,323	2,260	2,140	1,306	50
Mortality (%)	9.4	13.4	15.8	20.2	24.3	32.3
95% CI	8.3–10.5	12.1–14.7	14.4–17.1	18.7–21.8	22.7–26.0	29.5–35.1
Diabetes						
Number at risk	1,190	1,106	1,049	946	605	25
Mortality (%)	8.7	15.2	19.6	27.5	33.7	40.0
95% CI	7.2–10.3	13.2–17.1	17.4–21.7	25.0–29.9	31.1–36.4	37.0–43.1
Female						
No diabetes						
Number at risk	1,068	987	955	892	530	18
Mortality (%)	12.5	19.1	21.7	26.9	31.2	38.1
95% CI	10.6–14.3	16.9–21.3	19.4–21.3	24.4–29.4	28.5–33.8	34.4–41.7
Diabetes						
Number at risk	462	403	369	333	190	6
Mortality (%)	16.0	26.7	32.9	39.5	46.5	54.2
95% CI	12.9–19.1	23.0–30.4	29.9–36.8	35.7–43.5	42.2–50.8	48.7–59.7

Thereafter, there was an increasing trend of diabetes risk during observation time, and after approximately a quarter of a year, diabetic individuals had a higher mortality than nondiabetic individuals. After 3 years, the mortality risk tended to become equal. In women, the pattern was similar; however, there was no statistically significant time dependency. Age, renal failure (only in men), level of care dependency, number of prescribed drugs, and hemorrhagic stroke were significantly associated with mortality; however, they did not alter the association between diabetes and mortality. Our results remained almost unchanged in several sensitivity analyses, for example, using logistic regression models with the variable log(time) as well as time as a linear predictor (data not shown).

Looking for an explanation for our finding that mortality in the first 30 days after stroke was lower in diabetic men, one may find several possible hypotheses. First, one could argue that diabetic patients are more closely monitored by several specialists because of their chronic disease. They have more comorbidities, as indicated by medications and outpatient diagnoses; however, if problems arise, they might be identified and treated earlier. In Germany, nationwide disease management programs for diabetes have been implemented since 2003. These programs define contents and time frames for the treatment of diabetes

and its complications, as well as the associated cardiovascular risk factors. In this context, the observed larger number of prescribed medications in diabetic patients also might hint at more aggressive management of cardiovascular risk factors. The question remains, however, as to why diabetic men should have a higher benefit than diabetic women. Women with a stroke event are older than men and more likely to be in long-term care; hence, they might be less likely to be included in a disease management program (25). Furthermore, it might be that cardiovascular diseases in particular are treated earlier in younger patients and in men. Increasing age and female sex have been found to be related to a prolonged delay of emergency care in acute stroke events (26,27). This hypothesis is further supported by our observation that the impact of diabetes seems to differ between younger and older individuals. In stratified models, there was a more pronounced time dependency in individuals aged ≤70 compared with those >70 years. In individuals aged ≤70 years, mortality during the first 30 days was lower in diabetic compared with nondiabetic individuals in both men and women (even though the time dependency was significant only in men), while this was not the case in patients >70 (data not shown). Second, the type of stroke may play a role. Diabetic individuals were more likely to have an ischemic stroke. In previously published

series, patients with ischemic strokes had a lower case fatality (mortality during the first 28 or 30 days after stroke) than patients with a hemorrhage stroke, whereas in the period after 30 days, mortality was higher after ischemic strokes (28). Third, hypertension was more prevalent in diabetic persons. Previously known hypertension at the time of the stroke event has been reported to be significantly associated with a decreased mortality for both sexes, possibly explained by a better tolerance toward higher admission blood pressure in those individuals, which might be clinically more relevant for the early outcome of hemorrhagic than ischemic strokes (29,30). Fourth, other factors may play a role, such as a higher prevalence of obesity among diabetic individuals undergoing stroke compared with their nondiabetic counterparts (31). It is known that obesity and overweight have a potential protective effect in elderly stroke patients (32,33). These phenomena should have larger effects in men since the degree of obesity is commonly higher in men than in women. However, in our data, we have no information about detailed clinical or lifestyle variables and only limited information about history of coronary events, chronic heart failure, and renal function. Also, exact causes of deaths cannot be determined by our data.

In the period after 30 days, the mortality risk in individuals with diabetes compared with those without diabetes increased. The observation that in the 3 to 5 years after stroke there was no longer a difference in mortality between individuals with and without diabetes in both men and women may be due to a lack of power resulting from lower case numbers. However, it might be explained by the fact that individuals who survive 3 years are healthier, independent from their diabetes status.

Comparison with other studies
The mortality after 30 days (case fatality, 10.5%) as well as the 1-, 2-, and 5-year mortalities in our study (19.5, 25.1, and 37.3%, respectively) were well in line with the findings of other more recent studies and, as expected, lower than earlier studies. Case fatalities in the literature ranged between 10 and 22% (7,9,34), and 1- and 5-year mortalities were 27 and 53%, respectively (10). Only a few studies investigated mortality after stroke in diabetic and nondiabetic patients (10–12,35,36); however, these studies were in part clinic based and analyzed only single subtypes of stroke or shorter periods of follow-up. In the study
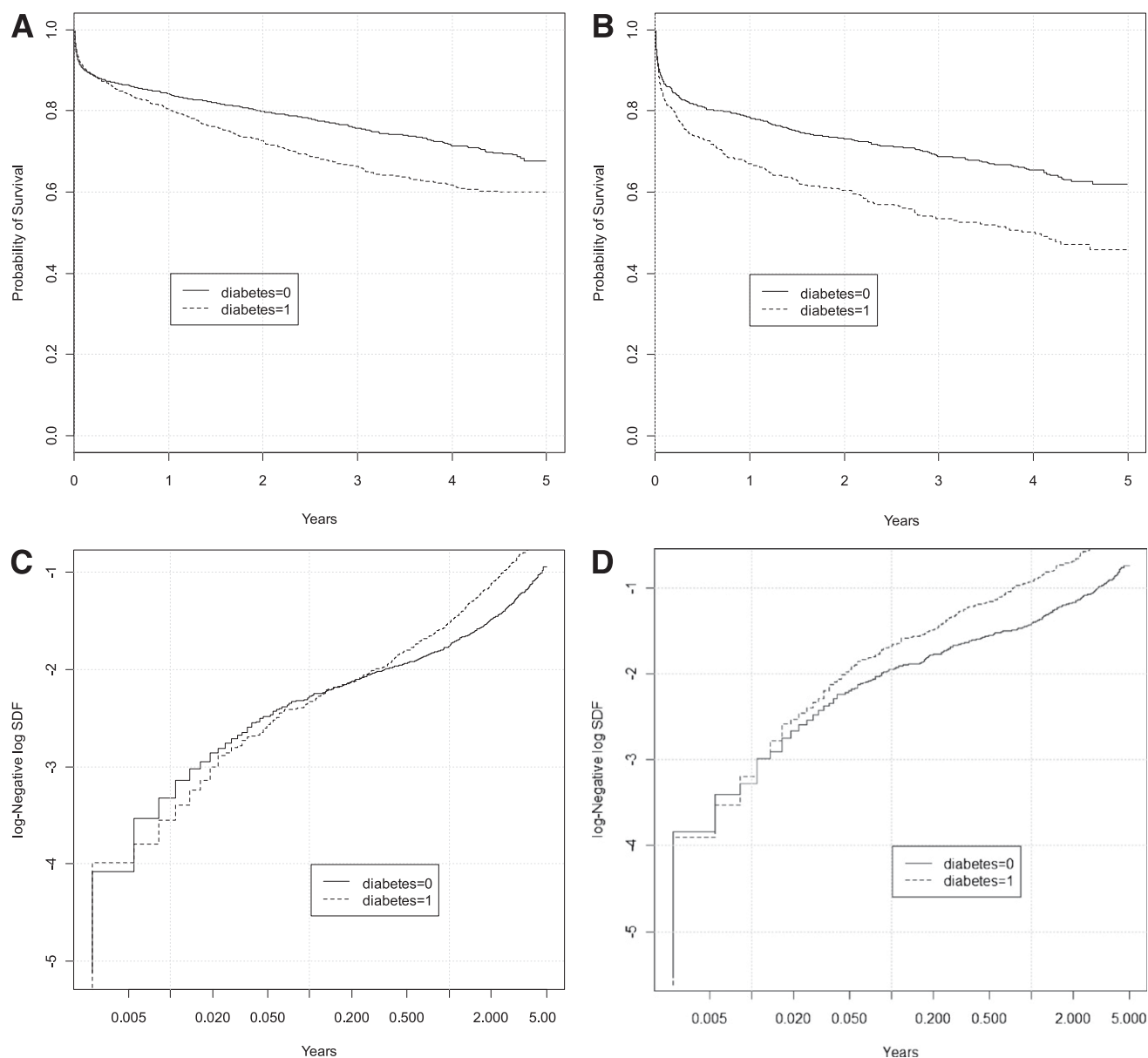
Figure 1—*A: Kaplan-Meier estimates of crude survival after first incident stroke for male GEK insurants, Germany, 2005–2007. B: Kaplan-Meier estimates of crude survival after first incident stroke for female GEK insurants, Germany, 2005–2007. C: Crude log-log survival curves after first incident stroke for male GEK insurants, Germany, 2005–2007. D: Crude log-log survival curves after first incident stroke for female GEK insurants, Germany, 2005–2007. SDF, survival distribution function.*

by Rautio et al. (10), only case fatality was investigated. During the period from 1985 to 1987, case fatality was 18% in diabetic and 15% in nondiabetic patients, with higher mortality in women than in men. However, in the period from 2000 to 2003, case fatality was ~15% in diabetic women, whereas in diabetic men as well as in nondiabetic men and women, it was ~10%. In our study, case fatality was ~9% in diabetic as well as nondiabetic men, and 16 and 13% in diabetic and non-diabetic women, respectively. Thus, we are in line with the Rautio et al. (10) study

that finds diabetic women have a higher excess risk to die within the first course after stroke; on the other hand, Rautio et al. (10) did not find lower risks for diabetic men. A further study analyzes the 3-month mortality in a clinic-based sample and finds diabetes to be a significant predictor of mortality (35).

To the best of our knowledge, there is no population- or insurance-based study that analyzes diabetic and nondiabetic patients for longer periods. Several studies evaluate diabetes as a predictor of mortality after incident stroke, but with

conflicting results. Although Hart et al. (8) found diabetes to be associated with mortality after stroke, Benatru et al. (7) and Petty et al. (9) did not find an association. Kamalesh et al. (11) analyzed the mortality after discharge from the hospital for a longer period, but only ischemic strokes were included in their study. Kaplan-Meier survival plots did not show a difference between individuals with and without diabetes during the first 60 days after discharge but did reflect lower survival in individuals with diabetes compared with those without diabetes after 1 year (11).

Table 3—*Predictors for mortality after first incident stroke, Cox regression GEK insurants during 2005–2007, stratified for sex*

	HR (95% CI) for death			
	Male population (n = 3,987)		Female population (n = 1,770)	
	Model 1	Model 2	Model 1	Model 2
Diabetes × 0–30 days	0.78 (0.63–0.98)*	0.67 (0.53–0.84)*	1.00 (0.77–1.30)	0.94 (0.72–1.23)
Diabetes × 30 days to 6 months	1.35 (1.01–1.79)*	1.14 (0.86–1.52)	1.31 (0.94–1.84)	1.25 (0.89–1.75)
Diabetes × 6 months to 1 year	1.61 (1.12–2.30)*	1.40 (0.97–2.00)	2.04 (1.26–3.31)*	1.98 (1.22–3.23)*
Diabetes × 1–2 years	1.60 (1.23–2.08)*	1.42 (1.09–1.85)*	1.14 (0.76–1.72)	1.12 (0.74–1.70)
Diabetes × 2–3 years	1.54 (1.13–2.10)*	1.39 (1.02–1.90)*	1.62 (1.02–2.58)*	1.63 (1.02–2.59)*
Diabetes × 3–5 years	1.06 (0.72–1.57)	1.00 (0.67–1.48)	1.08 (0.58–2.04)	1.10 (0.58–2.06)
Age (years) (continuously, per year)	1.06 (1.05–1.07)*	1.05 (1.04–1.05)*	1.06 (1.06–1.07)*	1.05 (1.04–1.06)*
Comorbidities				
Hypertension	—	0.83 (0.72–0.95)*	—	0.76 (0.64–0.92)*
Coronary heart disease	—	1.04 (0.91–1.18)	—	1.15 (0.97–1.37)
Renal disease	—	1.31 (1.11–1.54)*	—	1.11 (0.88–1.40)
Level of care dependency (baseline: 0)**				
1	—	2.06 (1.68–2.53)*	—	2.07 (1.65–2.59)*
2	—	2.32 (1.88–2.87)*	—	1.98 (1.57–2.49)*
3	—	3.36 (2.45–4.60)*	—	2.92 (2.08–4.10)*
Number of prescribed medications (continuously)	—	1.05 (1.04–1.06)*	—	1.02 (1.01–1.03)*
Subtype of stroke (baseline: cerebral infarction)				
Hemorrhage	—	2.40 (2.10–2.75)*	—	2.61 (2.15–3.16)*
Other/unknown	—	1.39 (1.14–1.69)*	—	1.31 (1.05–1.65)*

*$P < 0.05$. **0 = none; 1 = considerable; 2 = severe; and 3 = extreme.

The latter is in line with our results. Likewise, Gunarathne et al. (36) analyzed the 5-year mortality in individuals with and without diabetes after ischemic strokes. The 5-year mortality was significantly increased 1.6-fold in individuals with diabetes compared with those without diabetes; however, the study subjects were a clinic-based sample of migrant South Asian patients (36). Winell et al. (12) analyzed the 28-day and 1-year fatality after stroke, yet they included only ischemic strokes in their study. Both were significantly increased in individuals with diabetes compared with those without diabetes, without differences between men and women (12). 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 during the last years of observation and especially in women, the case numbers are low, leading to a lack of power to detect statistically significant differences between patients with and without diabetes. Second, we cannot exclude misclassification when we define patients with diabetes because our identification criteria had to be fulfilled within 12 months in the observation period between 2004 and 2007 and not solely

before the first stroke. On the other hand, diabetes is often identified for the first time in hospital stays as a result of typical complications, such as strokes, and these patients would not be classified as patients with diabetes if we used only the period before the event. However, we performed a sensitivity analysis, defining a person as having diabetes when our criteria were fulfilled within the 12 months before the first stroke. We found that approximately 9 of 10 diabetic patients already fulfilled our criteria before their index stroke. Furthermore, results of the mortality analysis remained unchanged. Third, we studied stroke survivors, and the number of fatal strokes may differ among those with and without diabetes. This may be an explanation for the reduced mortality seen within the first 30 days among patients with diabetes. However, on the basis of data from the German stroke registry as well as from several other countries, it can be assumed that the number of fatal strokes and strokes that are treated outside the hospital are small. Approximately 95% of stroke patients are hospitalized in clinics and, thus, identified by our data (40). Fourth, information about clinical variables (e.g., blood glucose and diabetes duration) and patient lifestyle (e.g., smoking and physical activities) is not available in the database. However, we included number

of prescribed drugs as well as outpatient diagnoses of relevant comorbidities and level of care dependency. Fifth, a translation of our results to other populations should be performed with caution since it is known that differences in morbidity as well as demographic and socioeconomic variables exist between health insurance funds (37,38). However, the incidence of stroke in our population was well in line with the incidence of stroke in a well-designed regional register-based study (2,39,40). Furthermore, the population has been used for several analyses regarding comorbidities in diabetes (2,13,14).

The main strength of our study is that we were able to analyze a large dataset without selection with respect to diabetes complications that could be followed up to 5 years.

In conclusion, in our German study, based on data from a nationwide health insurance fund, we found a high mortality in patients with a first stroke. It is interesting that the influence of diabetes was time dependent in men: in approximately the first quarter of a year after incident stroke, mortality was lower in diabetic than in nondiabetic individuals. Thereafter, diabetic patients had a higher mortality than nondiabetic patients, and after ~3 years, there was a convergence. In women, the pattern seems to be similar: no significant

time dependency was found. Our observation is in line with findings for mortality in diabetic compared with nondiabetic patients after beginning renal replacement therapy and amputation. Possible explanations may be differences in the type of stroke or in earlier and more intensive treatment of distinct cardiovascular risk factors in diabetic patients, in particular men. Patients that survive up to 3 years after stroke might be healthier, independent of their diabetes status. However, results remain conflicting, and further studies are warranted to confirm and explain the results.

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