Prognosis and Its Predictors After Incident Stroke in Patients With Type 1 Diabetes

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OBJECTIVE

Although patients with type 1 diabetes have a poor prognosis after a stroke, predictors of survival after an incident stroke in these patients are poorly studied.

RESEARCH DESIGN AND METHODS

In this observational study, a total of 144 patients of 4,083 with type 1 diabetes from the Finnish Diabetic Nephropathy (FinnDiane) Study suffered an incident stroke in 1997–2010, and were followed for a mean 3.4 ± 3.1 years after the stroke. Information was recorded on hard cardiovascular events and death as a result of cardiovascular or diabetes-related cause, collectively referred to as vascular composite end point. Information was collected from medical records, death certificates, and the National Care Register of Health Care. Predictors at the time of the incident stroke were studied for the end points.

RESULTS

During follow-up, 104 (72%) patients suffered a vascular composite end point. Of these, 33 (32%) had a recurrent stroke, 33 (32%) a hard cardiovascular event, and 76 (53%) died of cardiovascular or diabetes-related causes, with an overall 1-year survival of 76% and 5-year survival of 58%. The predictors of a vascular composite end point were hemorrhagic stroke subtype (hazard ratio 2.03 [95% CI 1.29–3.19]), as well as chronic kidney disease stage 2 (2.48 [1.17–5.24]), stage 3 (3.04 [1.54–6.04]), stage 4 (3.95 [1.72–9.04]), and stage 5 (6.71 [3.14–14.34]). All-cause mortality increased with deteriorating kidney function.

CONCLUSIONS

Patients with type 1 diabetes with an incident stroke have a poor cardiovascular prognosis and a high risk of all-cause mortality. In particular, hemorrhagic stroke subtype and progression of diabetic kidney disease conveys worse outcome.

The number of patients with type 1 diabetes is increasing worldwide. These patients also carry a markedly increased risk of stroke (1), and this risk materializes more than 10 years earlier than in subjects without diabetes (2). Although survival after a stroke has improved in the general population (3), only a few studies have investigated the survival of patients with type 1 diabetes and an incident stroke (4).

In the general population, the survival rate after an incident stroke is decreasing each year after by ~10%, with the cause of death usually being a recurrent stroke, a cardiovascular event, or complications as a result of the first stroke (5). The predictors of poor outcome after a stroke are male sex, ischemic heart disease, older age, and the presence of diabetes (6,7), with diabetes being one of the strongest predictors of poor

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outcome (8,9). In young patients with an incident ischemic stroke, type 1 diabetes independently increased the risk of 5-year mortality more than threefold (10). Compared with individuals without diabetes, patients with type 1 diabetes also experience a worse vascular prognosis after an incident ischemic stroke (11).

Despite the fact that type 1 diabetes increases the risk of premature mortality after a stroke in young patients, conspicuously few studies have explored the survival after an incident stroke in this patient group. According to a study by Secrest et al. (4), 87% of all patients with an incident stroke died within the next 3.8 years. This is a significantly higher mortality rate than in the general population (5,6). However, only 32 incident stroke cases were recorded in the study by Secrest et al. (4), which jeopardized any attempts to explore potential predictors of survival. In contrast, the Finnish Diabetic Nephropathy (FinnDiane) Study is large enough to provide the stage to explore such predictors in a reasonably large number of case subjects with sufficient follow-up time after the stroke.

We therefore aimed to study the prognosis of patients with type 1 diabetes who had suffered an incident stroke and, furthermore, to identify the predictors of survival after a stroke in these patients.

RESEARCH DESIGN AND METHODS

All patients were part of the FinnDiane Study, a nationwide multicenter study with the aim to uncover genetic, clinical, and environmental risk factors for micro- and macrovascular complications of type 1 diabetes. Type 1 diabetes was defined as diabetes diagnosis before 40 years of age and insulin medication commenced within 1 year after diagnosis. The study population consists of patients with type 1 diabetes from all over Finland. All adult patients with type 1 diabetes attending the 77 participating study centers' (Supplementary Data) diabetes and/or renal outpatient clinics were consecutively asked to participate in the study. The baseline visits began in 1998 and are still ongoing, and follow-up visits have been conducted since 2004. For this particular study, we included all 149 patients with type 1 diabetes and an incident stroke between 1997 and 2010, as described in detail previously (12). The local ethics committee of each center approved the study protocol, and the study was performed in accordance with the Declaration of Helsinki. Each participating patient signed an informed written consent.

Incident Stroke

A detailed description of the identification and classification of the incident strokes has previously been reported (12). In short, patients with an incident stroke during follow-up were identified from the FinnDiane questionnaires (either from the baseline visit or the follow-up visit), death certificates, and the National Care Register of Health Care based on the ICD-10 (codes I60-I64). Patients with a stroke before the FinnDiane baseline visit were excluded. On all patients with an incident stroke, medical records, computed tomography images, and magnetic resonance images were ordered from the hospitals where the patients had been treated for the stroke. Based on this information, two stroke neurologists (J.P. and R.L.) classified all the incident strokes presenting with clinical symptoms into either ischemic stroke or hemorrhagic stroke. Ischemic strokes were further subdivided into lacunar and nonlacunar infarctions (13).

Data at the Time of the Incident Stroke

Data prior to the incident stroke consisted of information on the patients' medical condition and history, medication, and lifestyle, collected from the FinnDiane baseline or follow-up visits. Data at the time of the incident stroke included HbA_{1c} values, creatinine concentrations, renal status, presence of coronary heart disease (CHD), medication, current smoking, age at stroke, as well as duration of diabetes at the time of stroke. These data were collected from medical records or death certificates or from the FinnDiane visits if no information could be obtained from the other two sources. Kidney status was defined based on the urinary albumin excretion rate (UAER), as well as the presence of end-stage renal disease (ESRD), and further divided into five groups: normal UAER, microalbuminuria, macroalbuminuria, kidney transplant, and dialysis treatment. A normal UAER was defined as <20 μg/min or <30 mg/24 h, microalbuminuria as a UAER ≥ 20 and <200 μg/min or ≥ 30 and <300 mg/24 h, and macroalbuminuria as a UAER ≥ 200 μg/min or ≥ 300 mg/24 h. Estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (14). CKD was defined based on the eGFR and divided into five stages: stage 1 was defined as an eGFR ≥ 90 mL/min/1.73 m^2, stage 2 as an eGFR ≥ 60–89, stage 3 as an eGFR ≥ 30–59, stage 4 as an eGFR ≥ 15–29, and stage 5 as an eGFR <15 or dialysis treatment. Severe diabetic retinopathy (SDR) was defined as retinal laser treatment. CHD was defined as a history of myocardial infarction or coronary artery revascularization or treatment with long-acting nitroglycerin. Medication included anticoagulation medication, antihypertensive medication, and lipid-lowering medication. Current smoking was defined as smoking of at least one cigarette per day.

Follow-up Data

Follow-up information after the incident stroke consisted of hard cardiovascular end points, such as acute myocardial infarction, coronary artery bypass surgery, coronary angioplasty, stroke, or death as a result of cardiovascular or diabetes-related cause, collectively referred to as a composite vascular end point. The information was collected from medical records, death certificates until August 2012, the FinnDiane database, and the National Care Register of Health Care, based on the ICD-10 by December 2011 for cardiovascular events, and by December 2012 for strokes. All events during follow-up were registered. Follow-up time was calculated from the date of the incident stroke until the date of the second stroke, first hard cardiovascular end point, or death, or until the last date the patients were known to be free of a composite end point, i.e., December 2011. We excluded 3 of the 149 incident stroke case subjects as a result of unclear information during follow-up. Two of the patients without an event during follow-up died of an unknown cause and were excluded. Thus, a total of 144 case subjects were included in the final analyses.

Statistical Analyses

All variables were tested for normal distribution. Parametric continuous variables were analyzed with the Student *t* test; results are presented as mean with SD. Nonparametric continuous variables were analyzed with the Mann-Whitney *U* test; results are presented as medians with interquartile range. The difference in categorical variables between groups was tested with the χ^2 test. In order to estimate the survival of the patients after the incident stroke, we performed

Kaplan-Meier survival plots for overall survival, survival based on incident stroke type, and survival based on renal status at the time of the stroke. According to the results of the univariate analyses or of the survival analyses, Cox proportional hazards analyses were performed and adjusted for incident stroke type, kidney status, and lacunar infarction in order to determine which factors independently affected the prognosis of the patients. The results are presented as hazard ratio (HR) with 95% CI. $P < 0.05$ was considered statistically significant. All analyses were performed with SPSS Statistics 23.0 (IBM Corporation, Armonk, NY).

RESULTS

Of the 149 patients with an incident stroke, there was complete information on 144 patients during follow-up. A total of 104 (72%) patients suffered from a composite end point during follow-up, whereas 40 (28%) patients were free of a composite event. The flowchart in Fig. 1 describes the follow-up events of the patients. During follow-up, 33 (32%) patients with a composite end point experienced a hard cardiovascular event, 33 (32%) experienced a recurrent stroke, and 8 (8%) experienced multiple strokes during follow-up. Of the patients with a composite end point, eight patients suffered from recurrent stroke as well as a cardiovascular event (CVD event) (Fig. 1). In total, 77 (53%) of the patients with an incident stroke died during follow-up, of whom 31 had experienced another hard cardiovascular end point before death. Of all patients, 76 (53%) died of a cardiovascular or diabetes-related death. The mean follow-up time to the composite end point was 3.4 ± 3.1 years, range 0.0–14.7 years (Fig. 1).

Figure 2*A* shows the overall survival after an incident stroke. Overall survival decreased steadily, with 1-year survival being76% and 5-year survival 58%. Figure 2*B* shows the survival stratified by incident stroke type, and survival was significantly poorer if the incident stroke was of hemorrhagic subtype; the 1-year survival was 52% for hemorrhagic stroke as compared with 87% for ischemic stroke ($P < 0.001$). For the 5-year survival, the difference in survival rates was decreased, survival being 46% for hemorrhagic stroke and 64% for ischemic stroke ($P = 0.038$). Survival also decreased significantly with deteriorating kidney function, as shown in Fig. 2*C*, with the 1-year survival for stage 1 being 87%, stage 2 88%, stage 3 81%, stage 4 64%, and stage 5 50% ($P = 0.008$), and the 5-year survival for stage 1 being 87%, stage 2 63%, stage 3 52%, stage 4 57%, and stage 5 30% ($P = 0.001$).

Table 1 shows the characteristics at the time of the first stroke of the patients with a composite end point during follow-up compared with patients without an event. The distribution of men and women was equal in both groups, the majority being men. The patients were also equally old at the time of the stroke and had similar age at onset of diabetes. The distribution of hemorrhagic strokes was the same, whereas lacunar infarctions were more common in those without any composite end point. Notably, ESRD was more common in those with a composite end point, as was also CKD stages 3 and 5. There were no differences in the presence of SDR or CHD or use of aspirin, antihypertensive medication, lipid-lowering medication, or warfarin. Also, no differences in current smoking or HbA_{1c} were seen, whereas in those with a composite end point, the creatinine concentrations were higher (Table 1).

In order to determine which factors independently affect the prognosis after a stroke, we performed Cox proportional hazards analyses, as shown in Table 2. In model 1, we adjusted for stroke type and renal status. A hemorrhagic stroke, having received a kidney transplant, or being on dialysis were all independent predictors of a composite end point. We also adjusted the models for kidney function based on eGFR, as well as kidney disease stages. Hemorrhagic stroke, lower eGFR, and CKD stages 2–5 were all independent predictors for a composite end point (Table 2, models 2 and 3).

Similar analyses were performed for the subtypes of ischemic stroke (lacunar or nonlacunar infarction). In these analyses, having received a kidney transplant, being on dialysis, lower eGFR, and CKD stages 2–5 were all independent predictors for a composite end point, with similar HRs as in the analyses for incident stroke (data not shown). Nonlacunar infarction was an independent predictor for a composite end point in the analysis adjusted for eGFR (HR 1.79 [95% CI 1.09–2.94]) and for CKD (1.99 [1.20–3.27]), but not in the analysis for renal status (1.58 [0.99–2.54]).

We performed similar subanalyses to determine potential predictors of other end points, such as CVD event, recurrent

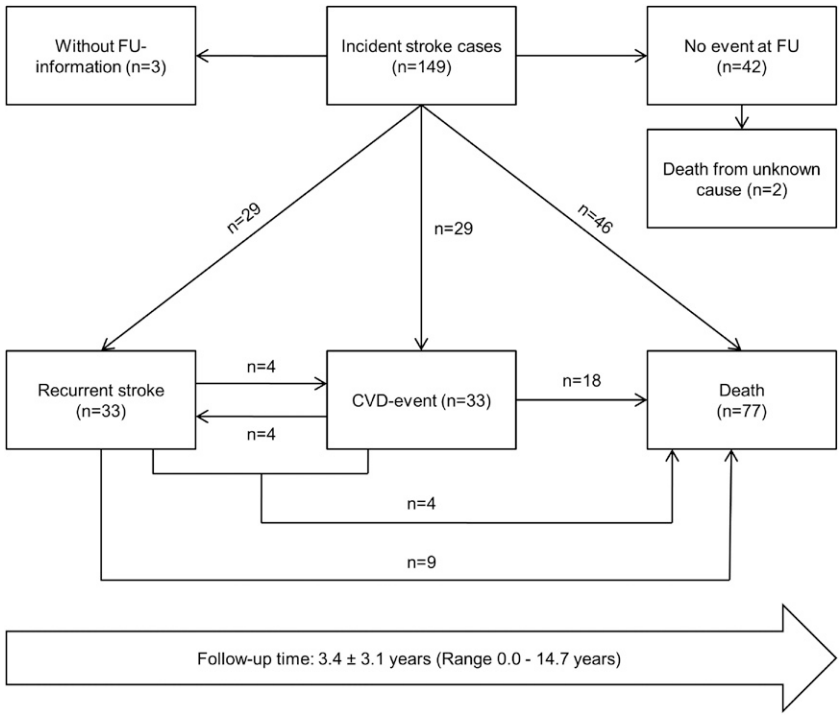

Figure 1—Flowchart of incident stroke case patients and events during follow-up. CVD-event, cardiovascular hard end point (acute myocardial infarction, coronary artery bypass surgery, or coronary angioplasty); FU, follow-up.

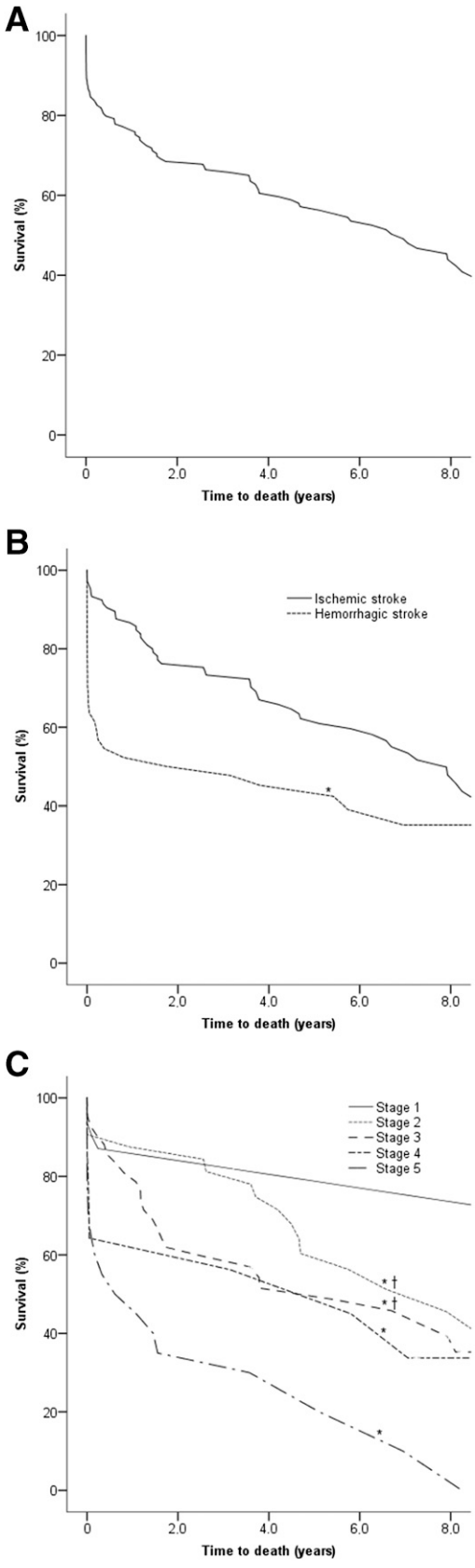

Figure 2—Survival after incident stroke. *A*: Overall survival after incident stroke. *B*: Survival stratified by incident stroke type. *$P < 0.05$, compared with incident ischemic stroke. *C*: Survival stratified by CKD stage. *$P < 0.05$, compared with stage 1; †$P < 0.05$, compared with stage 5.

stroke, or death. However, no predictors were found for recurrent stroke, whereas similar results as shown in Table 2 were found for CVD event or death as the end point (data not shown).

CONCLUSIONS

In this study, we show that patients with type 1 diabetes and an incident stroke have a high risk of cardiovascular complications, and that the overall survival of these patients is poor. As many as 53% of the patients died during a mean follow-up time of 3.4 years. In general, ischemic stroke was associated with a better survival than a stroke of the hemorrhagic subtype, especially during the first year of follow-up. A novel finding was that the independent predictors of a composite end point were hemorrhagic stroke subtype, worsening kidney function, and especially ESRD. Traditional predictors for a poor outcome after a stroke, such as CHD and male sex, were not significant in our study.

The prognosis after an incident stroke in patients with type 1 diabetes is poorly studied. Our results are in line with the study by Secrest et al. (4) that followed incident stroke case subjects for 4 years. In their study, 33% died of a recurrent stroke, 33% of a cardiovascular event, and 30% of a diabetes-related cause, numbers that are almost identical to the ones found in our study. In our study, the mortality rate was, however, lower: 53% compared with 87% in the study by Secrest et al. (4). The patient characteristics in both studies were similar, so the difference could be explained by, for example, differences in treatment strategies or the smaller number of patients, and, thus, lower power in the study by Secrest et al. (4).

In subjects without diabetes, 5-year mortality varies between 11 and 60%, depending on the age at the incident stroke (5,6,10), as well as the subtype of stroke. Hemorrhagic stroke usually has a higher cumulative risk of death, especially during the first year after a stroke (5,15). At the time of their index stroke, the patients in our study were markedly younger (mean 50.4 years), compared with patients with type 2 diabetes and the general population, in which most of the strokes occur between the age of 60 and 80 years (16,17) and 65 and 85 years, respectively (18,19). Despite the lower age at stroke, the duration of diabetes is longer in our patients, ~30 years, compared to 10

Table 1—Characteristics at the time of their first stroke of patients with no event compared with patients with composite end point during follow-up

Characteristics	No event (n = 40)	Composite end point (n = 104)	P
Men (%)	65	66	0.879
Age at onset of diabetes (years)	16.0 (8.0–26.0)	12.0 (7.0–19.5)	0.076
Age at stroke (years)	51.1 ± 9.5	50.4 ± 9.0	0.656
Duration of diabetes (years)	34.2 ± 8.9	36.2 ± 8.2	0.201
Incident hemorrhagic stroke (%)	23	31	0.325
Incident ischemic stroke (%)	78	69	0.325
Lacunar infarction	74	47	0.012
Nonlacunar infarction	26	53	0.012
History of TIA (%)	3	4	0.673
HbA_{1c} (%)	8.8 ± 1.3	8.8 ± 1.7	0.999
HbA_{1c} (mmol/mol)	72 ± 14	72 ± 18	0.999
Renal status (%)			
Normoalbuminuria	28	10	0.006
Microalbuminuria	25	13	0.067
Macroalbuminuria	30	21	0.263
Kidney transplant	15	40	0.004
Dialysis	3	16	0.024
ESRD (%)	18	57	<0.001
eGFR (mL/min/1.73 m^2)	91 (58–107)	44 (26–66)	<0.001
CKD (%)			
Stage 1 (eGFR ≥90)	51	12	<0.001
Stage 2 (eGFR 60–89)	23	22	0.879
Stage 3 (eGFR 30–59)	18	35	0.045
Stage 4 (eGFR 15–30)	5	13	0.203
Stage 5 (eGFR <15 or dialysis)	3	19	0.014
SDR (%)	75	86	0.133
CHD (%)	23	29	0.443
Atrial fibrillation (%)			
Prior	5	1	0.149
At diagnosis	0	2	0.375
Aspirin (%)	50	60	0.297
Warfarin (%)	5	5	0.971
Antihypertensive medication (%)	88	91	0.485
Lipid-lowering medication (%)	50	39	0.208
Current smoking (%)	23	26	0.766

Data are presented as mean ± SD or median with interquartile range, unless otherwise noted. Composite end point is recurrent stroke, cardiovascular hard event, or death by cardiovascular or diabetes-related cause. TIA, transient ischemic attack.

years in patients with type 2 diabetes (17). Compared with the general population, not only is the mortality rate higher in patients with type 1 diabetes, but death also occurs much earlier, giving these young patients a far worse prognosis after a stroke than for subjects free of diabetes.

In accordance with studies in the general population (8), we also found that hemorrhagic stroke is associated with a poorer outcome than stroke of ischemic origin. In most cases, a hemorrhage causes more extensive brain tissue damage, edema, and associated deleterious effects than a stroke of ischemic origin, thus leading to higher early mortality. The survival is, however, only poorer during the first months (20), and after 5 years, no differences are seen between these two subtypes of stroke (5,15). A similar decline in mortality was also seen in our study, with most of the deaths as a result of hemorrhagic strokes occurring during the first year after the stroke, and similar survival seen at ~8 years after the stroke.

We have shown previously that diabetic nephropathy and decreasing kidney function independently increase the risk of both ischemic and hemorrhagic strokes (21). In the current study, we could further show that kidney disease was the main determinant of poor survival after an incident stroke. Other available risk factors measured at the time of the first stroke did not affect the prognosis. Impaired kidney function has been associated with poor outcome after an incident stroke also in young subjects without diabetes (22), as well as in patients with type 2 diabetes (23). In patients with type 1 diabetes, diabetic nephropathy predicts both cardiovascular mortality and all-cause mortality (24,25). Our findings are in line with these studies. Not only is the risk of a premature death increased in these patients, but the risk of suffering a hard cardiovascular event is also increased. Moreover, a new finding is that the risk seems to be increased already at CKD stage 2 in these patients, whereas micro- or macroalbuminuria do not increase the risk.

In studies performed on subtypes of ischemic stroke (nonlacunar or lacunar infarction), nonlacunar infarction has been associated with a poorer outcome than lacunar infarction (26,27). In our study, nonlacunar infarction independently predicted poorer survival after an incident stroke. In nonlacunar infarction, brain lesions are more extensive than in lacunar infarction, leading to more outspread damage in the brain tissue and, therefore, a higher risk of a recurrent stroke or death.

One of the limitations of this study is the observational study setting. The clinical data at the time of the stroke were reviewed from medical files; thus, for example, no centrally measured laboratory data were available from the time of the incident stroke. We were, however, able to retrieve data on creatinine and HbA_{1c} at the time of the stroke on the majority of the patients. Thus, we cannot rule out that there could be other independent predictors of survival and confounding factors that we were not able to assess. Furthermore, we were unable to acquire information on treatment strategies during follow-up, and, therefore, the effect of secondary prevention could not be assessed. Another limitation is that the number of patients included in this study is small compared with studies in the general population. However, to this date, this is the largest existing study population of patients with type 1 diabetes and stroke, which enables us for the first time to study independent predictors of survival after an incident stroke in patients with type 1 diabetes. Another strength in our study is the well-characterized patient population. Only patients with complete data on follow-up were included, and all of the composite end points were confirmed from either

Table 2—Predictors of a composite end point during follow-up after an incident stroke

	Model 1	*P*
Incident hemorrhagic stroke (vs. ischemic stroke)	1.63 (1.06–2.51)	0.027
Renal status		
Normoalbuminuria (reference)	1.00	
Microalbuminuria	1.51 (0.66–3.46)	0.332
Macroalbuminuria	1.45 (0.69–3.07)	0.331
Kidney transplant	2.57 (1.27–5.17)	0.008
Dialysis	4.78 (2.16–10.60)	<0.001
	Model 2	*P*
Incident hemorrhagic stroke (vs. ischemic stroke)	2.40 (1.52–3.79)	<0.001
eGFR (mL/min/1.73 m^2), per unit increase	0.98 (0.97–0.99)	<0.001
	Model 3	*P*
Incident hemorrhagic stroke (vs. ischemic stroke)	2.03 (1.29–3.19)	0.002
CKD stage		
Stage 1 (reference)	1.00	
Stage 2	2.48 (1.17–5.24)	0.018
Stage 3	3.04 (1.54–6.04)	0.001
Stage 4	3.95 (1.72–9.04)	0.001
Stage 5	6.71 (3.14–14.34)	<0.001

Data are presented as HR (95% CI). Composite end point is recurrent stroke, cardiovascular hard event, or death by cardiovascular or diabetes-related cause.

medical records or death certificates. In Finland, virtually all patients with a hard cardiovascular end point are treated in hospitals, and if the patient dies outside a treatment facility, an autopsy is performed routinely to ascertain the cause of death. Therefore, we believe that no false events have been reported during follow-up. Furthermore, all the strokes included were confirmed and classified by the same neurologists using the same methodology.

In conclusion, we show here that the cardiovascular prognosis and overall survival after an incident stroke in patients with type 1 diabetes is poor, and that a hemorrhagic stroke is associated with a worse outcome than that of an ischemic stroke. For the first time, predictors of survival and prognosis after an incident stroke in type 1 diabetes could be elucidated, and hemorrhagic stroke, ESRD, and CKD stages 2–5 all independently increase the risk of a recurrent stroke, hard cardiovascular event, or death by cardiovascular or diabetes-related cause. Prevention of stroke, and especially of diabetes-related kidney disease, is therefore of great importance to improve the prognosis of patients with type 1 diabetes.

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Author Contributions. S.H.-H. had the main responsibility for analyzing the patient data and writing the paper. L.M.T. and J.P. contributed to study design, acquisition of data, data analysis, and critical revision of the paper. C.M.F. contributed to study design, acquisition of data, and critical revision of the paper. D.G., N.E., V.H., R.L., and T.T. contributed to study design and critical revision of the paper. P.-H.G. contributed to study design, acquisition of data, critical revision of the paper, and coordination of the study. P.-H.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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