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Predictors of and Survival after Incident Stroke in Type 1 Diabetes

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Abstract

Few studies have examined stroke risk in T1DM. Stroke incidence, predictors, and survival were thus explored. Pittsburgh EDC Study participants (n=658) with childhood-onset T1DM were followed biennially for 18 years. Baseline (1986–1988) mean age and diabetes duration were 28 and 19 years, respectively. Stroke incidence/type was determined via survey or physician interview and, when possible, confirmed with medical/autopsy records. During follow-up, 31 (4.7%) strokes occurred (21 ischemic, 8 hemorrhagic, 2 unclassified), mean age=40.2 years (range 23–60). In multivariable Cox modelling, diabetes duration, SBP, non-HDLc, WBC, and pulse significantly predicted ischemic stroke. Adding overt nephropathy (HR=4.4, 95% CI, 1.5–12.4) to the model replaced SBP. Survival after stroke was 80.6%, 45.2%, and 9.6% at 1, 5, and 10 years, respectively, significantly worse after hemorrhagic stroke (p=0.03). These risk factors merit careful evaluation and management to prevent stroke in T1DM, which occurs at least 20 years earlier than in the general population.

Introduction

Type 1 diabetes mellitus (T1DM) increases the risk for many long-term complications, especially renal and cardiovascular disease. Although many T1DM studies have included stroke as part of a composite cardiovascular endpoint, few have specifically focused on cerebrovascular disease in T1DM.[1–6]

Two recent studies have reported that T1DM does in fact increase the risk of stroke compared to nondiabetic persons, especially before 50 years of age.[5–7] Mortality from stroke is increased 3- to 4-fold in T1DM compared to the general population.[3] Prospective studies examining predictors of stroke in T1DM have shown that, univariately, conventional cardiovascular risk factors (i.e., hypertension and dyslipidemia), as well as proteinuria, increase stroke risk in this population.[1,2,4]

Using the Pittsburgh EDC cohort, our objectives were to: 1) determine the incidence of stroke in a large T1DM population; examine univariate and multivariable associations 2) between baseline variables and incident stroke, and 3) between time-varying variables and incident stroke; and 4) estimate median survival after incident stroke.

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Participants and Methods

Study population

Complete methodology for patient selection, examination, and laboratory testing in the Pittsburgh EDC Study has been described in detail.[8,9] Briefly, the EDC Study began in 1986–1988 consisting of 658 individuals diagnosed 1950–1980 with childhood-onset T1DM (age<17 years) and seen at Children's Hospital of Pittsburgh within 1 year of diagnosis. Mean age diabetes duration were 28 and 19 years, respectively, at baseline (1986–1988). Participants have been followed biennially by survey and/or examination. Research protocols were approved by the University of Pittsburgh Institutional Review Board, and all participants provided written informed consent.

Outcome variable

Incident stroke (as well as hospitalization for any reason) was assessed biennially via survey. Medical records were obtained, when possible, to verify stroke occurrence and type and were reviewed by a physician (TJO). Stroke was defined as a neurological deficit of acute onset lasting ≥24 hours without other evident cause.

Predictor variables

Blood pressure was measured with a random-zero sphygmomanometer after a 5-min rest according to the Hypertension Detection and Follow-up Program protocol.[10] Hypertension was defined as a blood pressure ≥140/90 mmHg or antihypertensive medication use. Height and weight were measured to calculate BMI. An ever smoker was defined as one who had smoked ≥100 lifetime cigarettes.

Fasting blood samples were taken to measure glycosylated hemoglobin (HbA_1), lipids, lipoproteins, and serum creatinine. Original HbA_1 values were converted to DCCT-aligned HbA_{1c} for all analyses. Total cholesterol and triglycerides were measured enzymatically, and HDL cholesterol was determined with a heparin and manganese chloride precipitation technique.[11] Non-HDL cholesterol was the difference between total and HDL cholesterol levels.

White blood cell counts were obtained using a Coulter Counter (model S-plus IV, Beckman-Coulter, Fullerton, CA) and fibrinogen using a biuret colorimetric procedure and a clotting method. Serum and urinary albumin were measured by immunonephelometry,[12] and creatinine was assayed using an Ectachem 400 Analyzer (Eastman Kodak, Rochester, NY). Renal damage status was based on urinary albumin excretion rates (AER) from two of three timed urine collections as follows: microalbuminuria, AER=20–200 μg/min; overt nephropathy, AER>200 μg/min or, in the absence of urine, a serum creatinine level >2 mg/dl, renal failure or renal transplantation. Glomerular filtration rate (GFR) was estimated using the Cockcroft-Gault equation.[13]

CAD was defined as CAD death, fatal or nonfatal myocardial infarction confirmed either by hospital records or Q-waves on electrocardiogram (Minnesota code 1.1, 1.2), angiographic stenosis ≥50% confirmed by hospital records, revascularization, EDC-diagnosed angina, or ischemic ECG changes (Minnesota code 1.3, 4.1–4.3, 5.1–5.3, 7.1). Lower extremity arterial disease (LEAD) included claudication (based on the Rose questionnaire), amputation, or ankle brachial index <0.8.[14]

Proliferative retinopathy (PR) was assessed using stereoscopic fundus photographs of fields 1, 2, and 4 with a Zeiss camera, read by the Fundus Photography Reading Center, University of Wisconsin-Madison and classified based on the modified Arlie House system.[15] PR was

defined as receiving laser phototherapy for proliferative diabetic retinopathy for participants refusing fundus photographs or unable to attend an EDC clinic visit (n=43).

Mortality data

Vital status was determined as of 1 January 2010 via participant contact and searches in both the Social Security Death Index and the National Death Index. Each death was confirmed by death certificate. In addition, attempts were made to obtain the following, if appropriate: pertinent medical records, autopsy/coroner's reports; and interview with next-of-kin regarding the circumstances surrounding the death. Each decedent's underlying cause of death, and all contributing causes, was determined by a Mortality Classification Committee of at least 2 physician epidemiologists using all available data based on standardized procedures.[16]

Statistical analysis

Baseline traditional cardiovascular and diabetes-specific risk factors were analyzed univariately using the Student's t test (or Mann-Whitney U for non-parametric comparisons) and the χ^2 test (or Fisher's exact test) by incident stroke status. Due to the small number of events, in addition to comparing ischemic stroke and no stroke, all incident strokes (ischemic and hemorrhagic) were combined for multivariable analysis. Significant univariate variables were made available to multivariable Cox regression models. The proportional hazards assumption was visually assessed, then verified by testing time-varying interaction terms.

Since many variables were significant univariately, exploratory analysis was performed by grouping variables into 3 groups: 1) demographic, 2) complications, and 3) clinical, with diabetes duration included in all exploratory models. Independent variables were analyzed both at baseline and as time-varying updated means. In the second method, updated means of each continuous variable were calculated as the overall mean of said variable for each participant at every cycle (i.e., the average of all data up to and including the present cycle), until either an event occurred or follow-up ended. Variables found to be significant in exploratory multivariable analysis were combined into Cox regression models with backward elimination. Survival plots by stroke status were based on Kaplan-Meier life-tables. Statistical significance was defined as p<0.05. All hazard ratios are reported per increase of 1 SD for continuous variables. SPSS 18.0 (IBM, Chicago, IL) was used for survival analyses and SAS 9.2 (SAS Institute, Cary, NC) for all other analyses.

Results

Four (0.6%) persons suffered a stroke prior to study entry and were excluded. In addition, one individual was lost to follow-up after the initial visit and thus excluded. During a mean (±SD) follow-up of 15.4 (±4.9 years), 31 participants (4.7%) suffered an incident stroke, six of which were fatal. This represents an unadjusted incidence rate of 3.1 (95% CI, 2.0–4.1) strokes/1000 person-years. The mean age at stroke onset was 40.2 years (range 23–60). Ten (32%) had evidence of coronary artery disease prior to the stroke, while 3 (10%) had a prior TIA. Stroke type was determined for 29 of the 31 incident strokes: 21 ischemic, 8 hemorrhagic, and 2 could not be classified.

Baseline predictors of stroke

Table 1 presents baseline data based on incident stroke status and type. Persons with incident stroke were significantly older and had a longer diabetes duration at baseline compared to no stroke, but no difference existed by sex or race. Baseline systolic blood pressure (SBP) was significantly higher for those with ischemic stroke, whereas diastolic

blood pressure was significantly higher for those with hemorrhagic stroke. Compared to individuals without stroke, non-HDL cholesterol (non-HDLc), triglycerides, albumin excretion rate (AER), fibrinogen, and white blood cell count were elevated, and estimated glomerular filtration rate (eGFR) was decreased, in those with ischemic stroke. Compared to those without stroke, pulse, non-HDLc, triglycerides, and AER were elevated, but daily insulin dose and hematocrit were decreased, in those with hemorrhagic stroke. HbA_{1c} was only univariately significant for hemorrhagic stroke. Of note, individuals with incident stroke (both types) were more likely to have a history of renal damage (microalbuminuria (MA) or overt nephropathy (ON)), but only those with ischemic stroke were more likely to have smoked.

Multivariable analyses of baseline predictors consistently showed diabetes duration and non-HDLc as significant predictors of any stroke, and their effects did not materially change in the four models (Table 2A). The effects of SBP and HBA_{1c} were only significant in Model 1, which also included a measure of renal function (eGFR). The effect of renal damage (ON) was highly predictive (HR=4.3), even after accounting for diabetes duration and non-HDLc, and replaced both SBP and HbA_{1c} (Table 2A, Model 2). Substituting subclinical renal damage (MA) for clinical ON was also predictive of stroke (HR=5.1, 1.5–18.1), as was the continuous measure, AER (HR=1.8, 1.2–2.6 per SD increase).

Consistent baseline predictors of ischemic stroke included diabetes duration, SBP, non-HDLc, WBC, and pulse (Table 2B). Unlike the overall stroke models in Table 2A, when ON was included (Table 2B, Model 4), these other baseline predictors remained significant, except for SBP.

Despite the small numbers, multivariable analysis revealed that the strongest baseline predictors of hemorrhagic stroke were diabetes duration (HR=3.5, 95% CI, 1.6–7.6), HbA_{1c} (HR=2.5, 1.4–4.5), and DBP (HR=2.0, 1.2–3.5).

Time-varying updated-means

Models using time-varying updated-means for all continuous variables were quite similar to the baseline models above. Predictors of incident stroke included longer diabetes duration (HR=1.57), higher SBP (HR=1.38), higher non-HDLc (HR=1.67), higher HbA_{1c} (HR=1.26), and lower eGFR (HR=0.50) (Supplemental Table 1, Model 1). When prevalent ON was added to the model, it was strongly predictive of stroke (HR=4.54) and replaced both SBP and non-HDLc. Both higher HbA_{1c} (HR=1.26) and lower eGFR (HR=0.53) remained in the fully-adjusted model (Suppl. Table 1, Model 2). The major predictors of ischemic stroke using time-varying updated-means were longer diabetes duration, ever smoker, higher SBP, and higher non-HDLc; however, neither diabetes duration nor ever smoker reached statistical significance (p=0.08 for both, Suppl. Table 1, Model 3). When prevalent ON was added, only longer diabetes duration (HR=1.70) and prevalent ON (HR=8.22) remained predictive in the final model (Suppl. Table 1, Model 4).

Survival after stroke

In this cohort, six (19.4%) incident strokes were fatal. The only significant baseline predictor of fatal incident stroke was HbA_{1c} (HR=2.3, 1.1–4.9); sex, diabetes duration, renal damage, hypertension, and dyslipidemia were not significant (data not shown). In participants with a non-fatal incident stroke (n=25), 40.0% suffered at least one additional stroke over a median follow-up time of 3.9 years (range 0.6–14.9). As of 1 January 2010, 27 (87.1%) individuals with an incident stroke had died. Overall median survival time after incident stroke was 3.8 years; 5.1 and 1.0 years for ischemic and hemorrhagic stroke, respectively. The underlying cause of death was as follows: 9 (33.3%) died of a stroke, 9

(33.3%) died of a myocardial infarction or CAD death, 8 (29.6%) died of another diabetes-related cause (e.g., diabetic ketoacidosis, end-stage renal disease, sepsis), and 1 (3.7%) died of multiple sclerosis. Of note, two individuals with a fatal hemorrhagic stroke had a prior ischemic stroke.

Survival after incident stroke is shown in Figure 1. Overall, 1-year survival after stroke was 80.6%; 5-year survival was 45.2%; and 10-year survival was 9.6%. Stratification by stroke type, despite limited numbers (hemorrhagic stroke, n=8), showed significant differences in survival, with 1-year survival after ischemic stroke at 95.2% vs. 50.0% for hemorrhagic stroke (p=0.03). A similar pattern persisted for 5-year survival (52.4% vs. 25.0%, respectively).

Discussion

We report that stroke incidence in a large childhood-onset T1DM population is 3.0/1,000 person-years during follow-up (mean 15.4 years), with no differences seen by sex. More than two-thirds of the incident strokes were ischemic, consistent with other studies,[2–4] and were usually not preceded by either CAD (32%) or TIA (10%), similar to the pattern seen in the general population. Baseline predictors of ischemic stroke included diabetes duration, SBP, pulse, non-HDLc, WBC, and renal measures; whereas, for hemorrhagic stroke, diabetes duration, DBP, and HbA_{1c} were significant. Renal damage, both at baseline and during follow-up, was the strongest predictor of overall and ischemic stroke in T1DM. Survival after stroke was low, especially for hemorrhagic stroke, consistent with findings that hemorrhagic strokes are often more severe.[17]

Very few reports exist on stroke in T1DM for comparison. The largest study to date, the Diabetes UK Study, of >23,000 individuals with insulin-treated diabetes (diagnosed prior to age 30) only examined fatal strokes.[3] The authors found overall stroke standardized mortality ratios of 3.1 for males and 4.4 for females. However, only 19% of our cohort had a fatal incident stroke, and >66% died of a cause other than stroke, so only capturing fatal strokes potentially misses a large segment of affected individuals.

The risk for any stroke in the U.K. General Practitioners Research Database Study was increased 3.7-fold for males and 4.8-fold for females with T1DM compared to matched controls.[6] In the Nurses' Health Study, the relative risk for hemorrhagic and ischemic stroke was 4.5 and 7.9, respectively, compared to non-diabetic women, over 24 years of follow-up.[5] Our incidence rate (4.7%) for any stroke in the EDC Study is approximately four times higher than that seen in the 20–59 year-old general population in NHANES 2005–2008 (1.2%).

Few data exist on predictors of stroke in T1DM. In 2001, Fuller et al. combined data from multiple countries to look at risk factors for stroke (fatal and non-fatal) in T1DM.[2] They found significant univariate associations between stroke and baseline SBP, ON, and ECG abnormalities, although the latter was only significant in men. However, a number of risk factors, including diabetes duration, plasma glucose, serum cholesterol, and smoking history, were not predictive. In contrast, diabetes duration was one of the strongest predictors in the present study. A more recent report from the Fremantle Diabetes Study found that the strongest univariate predictor of ischemic stroke in T1DM was serum HDL-cholesterol, with diabetes duration and history of blood pressure medication use also showing predictive value; however, only *five* incident ischemic strokes occurred in their cohort.[4] Both of these studies only explored univariate predictors of stroke.

Not surprisingly, we found different predictors for ischemic vs. hemorrhagic stroke. Diabetes duration, which, in childhood-onset diabetes serves as a proxy for age, strongly

predicted both types of stroke. Blood pressure was also a significant predictor for both, SBP for ischemic stroke and DBP for hemorrhagic stroke. Blood pressure has consistently been shown to be a risk factor for stroke both in T1DM[2,18] and in the general population.[19,20] It should be noted that SBP became non-significant with the addition of overt nephropathy to multivariable models of ischemic and overall stroke. The interplay between hypertension and derangements in the RAAS secondary to CKD are well known in both diabetes and the population at large,[21,22] and early and consistent use of RAAS inhibitors (ACE inhibitors and angiotensin II receptor blockers) have been shown to delay and/or prevent CKD in diabetes.[23,24] Similarly, increased non-HDL cholesterol levels predicted stroke in our population, and the timely addition of statin therapy for T1DM patients with dyslipidemia has shown clear antithrombotic benefit which translates into reduced rates of stroke.[25,26] WBC, as a marker of inflammation, was also predictive of ischemic stroke, as has been reported in the general population.[27–29] Baseline HbA_{1c} was only predictive of hemorrhagic strokes, and not ischemic strokes, in our T1DM cohort. These results are not surprising, given the pathophysiology of each stroke type. Hemorrhagic stroke results from weakened or damaged blood vessels, similar to microvascular renal and retinal disease seen in diabetes patients, both of which are strongly associated with chronic hyperglycemia.[30] However, similar to the ischemic stroke findings reported herein, we have shown previously that baseline HbA_{1c} is not as predictive of CAD (i.e., ischemic heart disease) as other insulin resistance-related factors.[31]

When strokes occur in T1DM, they appear to have more detrimental effects on overall health and survival than seen in the general population. In fact, our median survival after incident stroke of 3.8 years is nearly half the median survival of 7 years after incident stroke in individuals aged 65–74 in the general population.[19]

Our EDC cohort has several strengths for evaluating the predictors of incident stroke and survival after stroke, including its prospective design with biennial examinations prior to stroke, its long-term follow-up to ascertain mortality, and its detailed classification of cause of death, including death certificates, autopsy and hospital records and review by an expert committee, using a standardized protocol to determine the primary cause of death and to rank contributory causes.[16] Ascertainment of relevant demographic and clinical variables has allowed us to incorporate these into our analysis to minimize confounding. The longitudinal nature of the data also allows the assessment of the effect of progression from normoalbuminuria to renal disease on mortality. Renal disease classifications were based on multiple samples (and confirmed by persistence or progression at the next examination) using identical protocols throughout the study period. Our renal disease data are quite consistent with those published from the FinnDiane study, thus strengthening the overall validity, particularly given the different socioeconomic and healthcare backgrounds from which both cohorts derive.[32,33]

However, this study has its limitations. Our cohort is hospital-based, which may limit the generalizability of these results; however, a comparison of the EDC study population with the Allegheny County T1DM registry found our EDC cohort to be epidemiologically representative of the local T1DM population.[34] Also, relatively few (n=31) strokes occurred during 18 years of follow-up. While we feel this figure is accurate, we are limited in our analyses to simple univariate and multivariable Cox modelling. As MRIs were not available to detect subclinical stroke, these data only capture clinical strokes, thus presenting only part of the stroke picture. In addition, we were unable to gather sufficient clinical data (especially hospital records from strokes occurring in the 1980s and 1990s) to adequately explore predictors of survival after stroke. Finally, the EDC population consists of participants with long-standing diabetes. Thus, these findings partially reflect outdated diabetes management and care, and may not be generalizable to individuals recently diagnosed with T1DM, whose

experience may more closely resemble that of the DCCT intensive therapy cohort, as recently described.[35]

As with the general population, stroke in T1DM is largely ischemic and usually not preceded by either a CAD or TIA event. The strongest predictors of stroke in T1DM were diabetes duration and modifiable risk factors, including increased blood pressure (ischemic and hemorrhagic), dyslipidemia (ischemic), poor glycemic control (hemorrhagic), and overt nephropathy (ischemic). Thus, careful diabetes management could minimize or prevent this major complication, which occurs at least 20 years earlier than in the general population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

AER	albumin excretion rate
BMI	body mass index
CAD	coronary artery disease
CI	confidence interval
CKD	chronic kidney disease
DBP	diastolic blood pressure
DCCT	Diabetes Complications and Control Trial
EDC	Epidemiology of Diabetes Complications
GFR	glomerular filtration rate
HDLc	high-density lipoprotein cholesterol
HR	hazard ratio
LEAD	lower extremity arterial disease
ON	overt nephropathy
PR	proliferative retinopathy
RAAs	renin-angiotensin-aldosterone system
SBP	systolic blood pressure
T1DM	type 1 diabetes mellitus
TIA	transient ischemic attack
WBC	white blood cells

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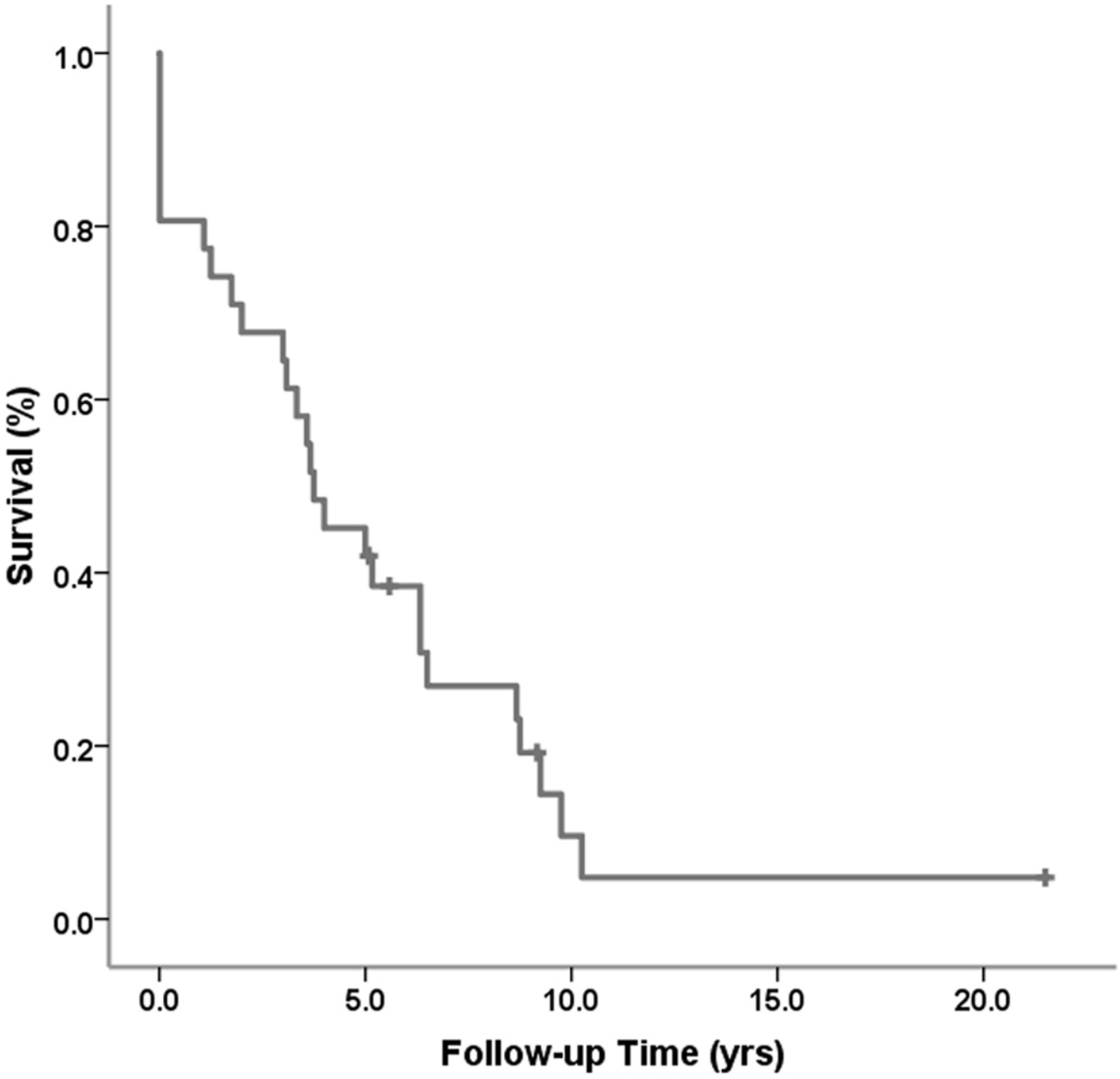

Figure 1.
Survival (Kaplan-Meier) after incident stroke in type 1 diabetes participants of the Pittsburgh EDC Study.

Table 1

Baseline characteristics (mean (±SD), % (*n*), or median (interquartile range)) of Pittsburgh EDC participants by incident stroke status (*n*=651)[†]

	No stroke	Incident ischemic stroke	Incident hemorrhagic stroke
N	623	21	8
Age (yrs)	27.3 (±7.8)	31.6 (±8.7)[*]	34.6 (±6.6)[**]
Diabetes duration (yrs)	19.0 (±7.4)	24.5 (±7.3)[***]	25.8 (±5.4)[**]
Female (%)	49.3 (307)	52.4 (11)	50.0 (4)
African-American (%)	2.2 (14)	0.0 (0)	12.5 (1)
HbA_{1c} (%)	8.7 (±1.5)	9.1 (±1.8)	10.0 (±1.7)[*]
Daily insulin dose (units/kg)	0.79 (±0.24)	0.89 (±0.42)	0.58 (±0.12)[*]
Systolic BP (mmHg)	113.2 (±15.5)	123.6 (±14.1)[**]	122.5 (±15.8)
Diastolic BP (mmHg)	72.6 (±10.9)	75.7 (±13.2)	82.6 (±12.8)[*]
BP medication use (%)	4.7 (28)	15.0 (3)	25.0 (2)[*]
Hypertension (%)	15.0 (93)	28.6 (6)	37.5 (3)
Pulse (beats/min)	78.3 (±9.9)	75.1 (±9.4)	89.3 (±9.9)[**]
Body mass index (kg/m^2)	23.5 (±3.2)	24.4 (±3.5)	22.0 (±2.4)
Waist-hip ratio	0.82 (±0.07)	0.85 (±0.09)	0.85 (±0.11)
HDL cholesterol (mg/dL)	53.9 (±12.4)	54.4 (±11.8)	50.4 (±11.5)
Non-HDL cholesterol (mg/dL)	135.4 (±41.7)	171.1 (±53.1)[***]	173.9 (±52.5)[**]
Triglycerides (mg/dL)	81.0 (60.0–120.0)	121.0 (79.0–186.0)[**]	201.0 (89.8–266.8)[**]
Estimated GFR (ml min^{-1} 1.73 m^{-2})	113.5 (±43.6)	90.1 (±36.9)[*]	76.3 (±51.7)[*]
Albumin excretion rate (μg/min)	15.2 (7.3–124.4)	358.5 (30.7–1274)[***]	246.3 (91.1–531.2)[*]
Serum Albumin (g/dL)	4.63 (±0.65)	4.24 (±0.65)[**]	4.45 (±0.51)
Serum Creatinine (mg/dL)	0.90 (0.70–1.10)	1.00 (0.80–1.10)	1.10 (0.58–4.08)
Fibrinogen (mg/dL)	270.0 (225–330)	320.0 (278–375)[**]	340.0 (248–420)
White blood cell count (× 10^9/L)	6.55 (±1.88)	8.31 (±2.43)[***]	5.61 (±1.43)
Hematocrit (%)	44.3 (±4.7)	43.7 (±5.8)	40.6 (±6.9)[*]
Prevalent CAD (%)	7.2 (45)	14.3 (3)	25.0 (2)
Prevalent LEAD (%)	11.2 (70)	23.8 (5)	25.0 (2)
Prevalent Microalbuminuria (%)	45.6 (284)	90.5 (19)[***]	87.5 (7)[*]
Prevalent Overt Nephropathy (%)	23.6 (147)	66.7 (14)[***]	62.5 (5)[*]
Prevalent Proliferative Retinopathy (%)	29.8 (182)	52.4 (11)[*]	50.0 (4)
Ever smoker (%)	37.1 (225)	66.7 (14)[**]	37.5 (3)

[†]Excludes 4 prevalent cases and 2 unclassified strokes and 1 lost-to-follow-up Incident stroke vs. no stroke:

[*]$p \leq 0.05$;

** $p \leq 0.01$;

*** $p \leq 0.001$

Abbreviations: BP, blood pressure; CAD, coronary artery disease; GFR, glomerular filtration rate; HDL, high density lipoprotein; LEAD, lower extremity arterial disease; Non-HDL, non-high density lipoprotein

Table 2

Cox regression models for baseline predictors of (A) any stroke and (B) ischemic stroke in type 1 diabetes.

	(A) Incident stroke		
	SD	**Model 1**	**Model 2**
Diabetes duration	7.508	1.87 (1.21–2.87) **	2.01 (1.33–3.03) ***
SBP	15.984	1.39 (1.03–1.86) *	Not selected
Non-HDLc	43.117	1.58 (1.17–2.13) **	1.50 (1.11–2.02) **
HbA_{1c}	1.532	1.46 (1.02–2.09) *	Not selected
eGFR	44.274	0.58 (0.36–0.91) *	Not selected
Prevalent ON		–	4.33 (1.85–10.1) ***
AIC (no covariates)[a]		325.2 (366.1)	324.1 (366.1)
	(B) Incident ischemic stroke only		
	SD	**Model 3**	**Model 4**
Diabetes duration	7.508	1.63 (1.00–2.67) *	1.66 (1.02–2.70) *
SBP	15.984	1.56 (1.05–2.31) *	Not selected
Non-HDLc	43.117	1.66 (1.15–2.39) **	1.50 (1.03–2.19) *
WBC	1.917	1.64 (1.14–2.36) **	1.58 (1.08–2.31) *
Pulse	9.970	0.55 (0.34–0.88) *	0.53 (0.32–0.88) *
Prevalent ON		–	4.37 (1.54–12.4) **
AIC (no covariates)[a]		213.8 (239.2)	209.6 (239.2)

Values shown are hazard ratios (95% CI), which are per 1 SD increase.

Model 1 allowed for diabetes duration, systolic blood pressure (SBP), non-HDL cholesterol (non-HDLc), HbA_{1c}, glomerular filtration rate (eGFR), ever smoker, and prevalent lower extremity arterial disease.

Model 2 allowed for Model 1 variables + prevalent overt nephropathy (ON).

Model 3 allowed for diabetes duration, SBP, non-HDLc, white blood cell count (WBC), pulse, eGFR, and ever smoker.

Model 4 allowed for Model 3 variables + prevalent ON.

* $p \leq 0.05$;

** $p \leq 0.01$;

*** $p \leq 0.001$

[a] AIC, Akaike's Information Criterion, for models 1 and 2, n=642 with 31 events, and for models 3 and 4, n=628 with 21 events