

Long-Term Risk of Stroke in Patients With Type 1 and Type 2 Diabetes Following Coronary Artery Bypass Grafting

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Background—We performed a nationwide population-based cohort study to investigate the long-term risk of stroke after coronary artery bypass grafting in patients with type 1 and type 2 diabetes.

Methods and Results—All patients who underwent primary coronary artery bypass grafting in Sweden from 2000 through 2011 were included from the SWEDEHEART register. We excluded patients with prior stroke, and patients who had a stroke or died within 30 days of surgery. The National Diabetes Register was used to identify patients with type 1 and type 2 diabetes. Incident stroke (ischemic and hemorrhagic), and all-cause mortality was obtained by record linkage with the National Patient Register and the Cause of Death register. We used multivariable Cox regression to estimate the risk of stroke in relation to type of diabetes. A total of 53 820 patients (type 1 diabetes [n=7 14], type 2 diabetes [n=10 054], no diabetes [n=43 052]) were included. During a mean follow-up of 7.4 years (398 337 person-years), in total, 8.0% (n=4296) of the patients had a stroke: 7.3% (n=52) in patients with type 1 diabetes, 9.1% (n=915) in patients with type 2 diabetes, and 7.7% (n=3329) in patients with no diabetes. The multivariable adjusted hazard ratio (95% CI) for all stroke was 1.59 (1.20–2.11) in type 1 diabetes, and 1.32 (1.23–1.43) in type 2 diabetes.

Conclusions—The long-term risk for stroke after coronary artery bypass grafting was increased in patients with type 1 and type 2 diabetes, compared to patients with no diabetes. (*J Am Heart Assoc.* 2015;4:e002411 doi: 10.1161/JAHA.115.002411)

Key Words: coronary artery bypass graft surgery • coronary artery disease • diabetes mellitus • long-term follow-up • stroke

Rates of cardiovascular disease (CVD) such as myocardial infarction and stroke among patients with diabetes have declined substantially the last 2 decades, where the magnitude of reduction is greatest for myocardial infarction.¹ Prevention of CVD by a combination of lifestyle changes, and lowering blood glucose, blood pressure, and lipid levels, both in type 1^{2,3} and type 2 diabetes may explain a large part of this reduction.^{4,5}

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The more rapid decline in myocardial infarction might partly be explained by improvements in interventional cardiology, but also because of improved pharmacological therapy.¹ Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are currently the available options for revascularization in patients with coronary artery disease. For diabetes patients, the results of most studies have favored CABG over PCI as the preferred method for revascularization, especially in multivessel disease.^{6,7} In the Strategies For Multivessel Revascularization in Patients with Diabetes (FREEDOM) trial, the hypothesis of CABG being more favorable than PCI with drug-eluting stents among diabetes patients for long-term outcome was tested.⁸ The risk of all-cause mortality and myocardial infarction was significantly lower in patients who underwent CABG compared to those who underwent PCI.⁸ However, the stroke rate, on the other hand, was higher in the CABG group.⁹ The reason for a higher stroke incidence after CABG is not known but may reflect higher prevalence of cerebral vascular disease in patients with diabetes.

To the best of our knowledge, no previous study has reported on the association between type 1 and type 2 diabetes and long-term risk of stroke after CABG.

We performed a nationwide population-based cohort study to investigate the long-term risk of stroke in patients with type 1 and type 2 diabetes compared to patients without diabetes.

Table 1. Baseline Characteristics in 53 820 Patients Who Underwent Coronary Artery Bypass Surgery in Sweden During 2000–2011 According to Diabetes Type

	All Patients	No Diabetes	Diabetes Type 1	Diabetes Type 2	P Value
Number of patients, %	53 820	43 052 (80%)	714 (1%)	10 054 (19%)	
Age, mean (SD)	67.36 (9.43)	67.52 (9.54)	56.80 (9.64)	67.42 (8.46)	<0.001
Female sex	11 874 (22%)	9234 (21%)	313 (44%)	2327 (23%)	<0.001
Birth region					
Nordic countries	49 158 (91%)	39 560 (92%)	695 (97%)	8903 (89%)	<0.001
Other	4657 (9%)	3487 (8%)	19 (3%)	1151 (11%)	<0.001
Education					
<10 years	23 480 (46%)	18 545 (45%)	226 (32%)	4709 (49%)	<0.001
10 to 12 years	19 375 (38%)	15 383 (38%)	334 (47%)	3658 (38%)	<0.001
>12 years	8447 (16%)	6977 (17%)	150 (21%)	1320 (14%)	<0.001
Marital status					
Married	35 627 (66%)	28 637 (67%)	426 (60%)	6564 (65%)	<0.001
Other	18 193 (34%)	14 415 (33%)	288 (40%)	3490 (35%)	<0.001
Household disposable income (tertiles)					
T1 (lowest)	17 454 (32%)	13 848 (32%)	197 (28%)	3409 (34%)	<0.001
T2	17 783 (33%)	14 147 (33%)	201 (28%)	3435 (34%)	<0.001
T3 (highest)	18 556 (34%)	15 030 (35%)	316 (44%)	3210 (32%)	<0.001
Body mass index, kg/m ² , mean (SD)	27.14 (4.01)	26.79 (3.86)	25.95 (4.09)	28.72 (4.25)	<0.001
eGFR					
>60 mL/min per 1.73 m ²	37 762 (76%)	30 241 (77%)	424 (63%)	7097 (75%)	<0.001
45 to 60 mL/min per 1.73 m ²	8211 (17%)	6532 (17%)	104 (15%)	1575 (17%)	<0.001
30 to 45 mL/min per 1.73 m ²	2712 (5%)	2022 (5%)	53 (8%)	637 (7%)	<0.001
15 to 30 mL/min per 1.73 m ²	528 (1%)	373 (1%)	29 (4%)	126 (1%)	<0.001
End-stage renal disease	420 (1%)	303 (1%)	65 (10%)	52 (1%)	<0.001
Hypertension	17 343 (32%)	12 596 (29%)	292 (41%)	4455 (44%)	<0.001
Hyperlipidemia	12 172 (23%)	9296 (22%)	180 (25%)	2696 (27%)	<0.001
Peripheral vascular disease	3940 (7%)	2914 (7%)	132 (18%)	894 (9%)	<0.001
Prior PCI	7886 (15%)	6164 (14%)	131 (18%)	1591 (16%)	<0.001
Chronic pulmonary disease	3397 (6%)	2599 (6%)	27 (4%)	771 (8%)	<0.001
Prior myocardial infarction	26 440 (49%)	20 785 (48%)	369 (52%)	5286 (53%)	<0.001
Left ventricular ejection fraction					
>50%	25 887 (69%)	20 648 (70%)	347 (69%)	4892 (64%)	<0.001
30 to 50%	9929 (26%)	7501 (25%)	128 (26%)	2300 (30%)	<0.001
<30%	1878 (5%)	1420 (5%)	25 (5%)	433 (6%)	<0.001
Heart failure	7103 (13%)	5366 (12%)	124 (17%)	1613 (16%)	<0.001
Atrial fibrillation	4727 (9%)	3780 (9%)	20 (3%)	927 (9%)	<0.001
History of cancer	3039 (6%)	2448 (6%)	28 (4%)	563 (6%)	0.125
Alcohol dependency	1012 (2%)	821 (2%)	7 (1%)	184 (2%)	0.179
Type of surgery					
Isolated CABG	46 432 (86%)	36 886 (86%)	674 (94%)	8872 (88%)	<0.001
CABG+valve	6996 (13%)	5809 (13%)	40 (6%)	1147 (11%)	<0.001

Continued

Table 1. Continued

	All Patients	No Diabetes	Diabetes Type 1	Diabetes Type 2	P Value
CABG+other	392 (1%)	357 (1%)	0 (0%)	35 (0%)	<0.001
Mechanical heart valve	1348 (3%)	1085 (3%)	12 (2%)	251 (2%)	0.362

Data are shown as n (%) unless otherwise noted. End-stage renal disease was defined as eGFR <15 mL/min per 1.73 m² or on dialysis/renal transplant. CABG indicates coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention.

Methods

This was a nationwide population-based observational cohort study, and it was approved by the regional Human Research Ethics Committee, Stockholm, Sweden. The need for informed consent was waived.

Study Population and Data Sources

We included all patients who underwent primary nonemergent CABG in Sweden from the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) register.^{10–12} We excluded patients with a history of stroke, patients with prior cardiac surgery, patients who underwent emergency surgery (within 24 hours of decision to operate), and patients who had a stroke or died within 30 days of surgery. The data from the SWEDEHEART register were combined with information from the National Diabetes Register¹³ using the unique Swedish personal identity numbers,¹⁴ as previously described.¹⁵ Record linkages were performed by the Swedish National Board of Health and Welfare and data were anonymized according to regulations. The National Patient Register¹⁶ was used to obtain prior diagnoses, and The Longitudinal integration database for health insurance and labor market studies¹⁷ was used to retrieve educational level, household disposable income, country of birth, and marital status.

Definition of Diabetes

In the Swedish National Diabetes Register, the epidemiological definition of type 1 diabetes was onset of diabetes before the age of 30 years and treatment with insulin only, and type 2 diabetes was defined as diabetes treated with diet or oral hypoglycemic agents alone, or age of ≥40 years at onset of diabetes and treatment with insulin alone or in combination with oral hypoglycemic agents.¹³

Outcomes

Follow-up started on January 1, 2000 and ended on December 31, 2012. We only used the first hospital admission for stroke

in patients with multiple stroke admissions. The following International Classification of Diseases (ICD) codes for a primary discharge diagnosis was used to identify incident stroke: all stroke (ICD codes I60 to I64), ischemic stroke (ICD codes I63 to I64), and hemorrhagic stroke (ICD codes I60 to I62). The validity of stroke diagnosis in the National Patient Register had been shown to be high.¹⁶ The Cause of Death Register was used to ascertain dates of death.

Statistical Analyses

Baseline characteristics were described as frequencies and percentages for categorical variables and means and standard deviations for continuous variables. Differences in baseline characteristics between patients with and without diabetes were compared using analysis of variance or χ^2 test. Person-time in days was counted from the date of surgery until the date of incident stroke, death, or the end of follow-up (December 31, 2012). For the analysis of the stroke outcome, patients who died during follow-up were censored on the date of death. We used Cox regression to estimate the risk of incident stroke, all-cause mortality, and a combined end point (stroke or all-cause mortality) in patients with type 1 diabetes or type 2 diabetes compared with patients without diabetes. The adjusted Cox models included all the variables listed in Table 1 as covariates and the models were stratified by calendar year of surgery and hospital. Patient age and body mass index was modeled using restricted cubic splines, and all other variables were included as categorical terms.

Missing data (educational level [4.7%], left ventricular ejection fraction [30%], renal function [7.8%], and body mass index [9.2%]) were handled by multiple imputation by chained equations.¹⁸ The imputation models included all variables in Table 1, and also the event indicator and the Nelson–Aalen estimator of the cumulative baseline hazard.¹⁹ Separate imputation models were used for the stroke and death outcomes. Ten data sets were imputed and estimates from these data sets were combined according to Rubin's rules. Missing data for country of birth (5 patients), household disposable income (27 patients), and marital status (27 patients) were imputed with the most common category.

Data management and statistical analyses were performed using Stata 14.0 (Stata Corp, College Station, TX) and R

Table 2. Long-Term Event Rates and Relative Risks for Stroke in Patients Who Underwent Coronary Artery Bypass Surgery According to Diabetes Type

Outcome	Events/Person-Years	Incidence Rate Per 1000 Person-Years (95% CI)	Age-Adjusted Hazard Ratio (95% CI)	P Value	Multivariable Adjusted* Hazard Ratio (95% CI)	P Value
All stroke						
No diabetes	3329/324 569	10.3 (9.9–10.6)	1.00 (Ref.)		1.00 (Ref.)	
Type 1 DM	52/5099	10.2 (7.8–13.4)	1.68 (1.27–2.21)	<0.001	1.59 (1.20–2.11)	0.001
Type 2 DM	915/68 669	13.3 (12.5–14.2)	1.33 (1.24–1.43)	<0.001	1.32 (1.23–1.43)	<0.001
Ischemic stroke						
No diabetes	2848/326 902	8.7 (8.4–9.0)	1.00 (Ref.)		1.00 (Ref.)	
Type 1 DM	42/5135	8.2 (6.0–11.1)	1.59 (1.17–2.16)	0.003	1.51 (1.10–2.06)	0.010
Type 2 DM	814/69 050	11.8 (11.0–12.6)	1.39 (1.28–1.50)	<0.001	1.37 (1.26–1.48)	<0.001
Hemorrhagic stroke						
No diabetes	592/338 371	1.7 (1.6–1.9)	1.00 (Ref.)		1.00 (Ref.)	
Type 1 DM	11/5293	2.1 (1.2–3.8)	1.90 (1.04–3.48)	0.038	1.82 (0.98–3.38)	0.056
Type 2 DM	124/72 135	1.7 (1.4–2.0)	1.01 (0.83–1.22)	0.946	1.02 (0.84–1.25)	0.825

DM indicates diabetes mellitus.

*Model included all variables reported in Table 1.

version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study Population and Patient Characteristics

A total of 53 820 patients (mean age 67 years, 22% women) who underwent isolated CABG (n=46 432), or CABG and heart valve surgery (n=6996), or CABG in combination with another cardiac procedure (n=392) from 2000 to 2011 were identified from the SWEDEHEART register. Patient characteristics according to type of diabetes are presented in Table 1. Patients with type 1 diabetes (714/53 820, 1%) were ≈10 years younger than patients with type 2 diabetes (10 054/53 820, 19%) and patients without diabetes (43 052/53 820, 80%). Patients with type 1 diabetes were more often female, more likely to have chronic kidney disease or end-stage renal disease, and more likely to have peripheral vascular disease compared to patients with type 2 diabetes or no diabetes. Atrial fibrillation was less common in patients with type 1 diabetes (3%) compared to patients with type 2 diabetes (9%) or no diabetes (9%).

Long-Term Risk of Stroke

During a mean follow-up time of 7.4 (SD 3.5) (median 7.7) years (398 337 person-years), in total, 8.0% (4296 of 53 820) of the patients had a stroke: 7.3% (52 of 714) of the patients with type 1 diabetes, 9.1% (915 of 10 054) of the patients

with type 2 diabetes, and 7.7% (3329 of 43 052) of the patients with no diabetes (Table 2). The age-adjusted stroke rate according to type of diabetes is shown in Figure.

The crude incidence rate of all stroke, ischemic stroke, and hemorrhagic stroke, respectively, are shown in Table 2.

The risk for stroke was significantly higher in patients with type 1 and type 2 diabetes compared with patients without diabetes in the age-adjusted and multivariable adjusted analyses (Table 2). After multivariable adjustment for all variables reported in Table 1, the hazard ratio (95% CI) for all

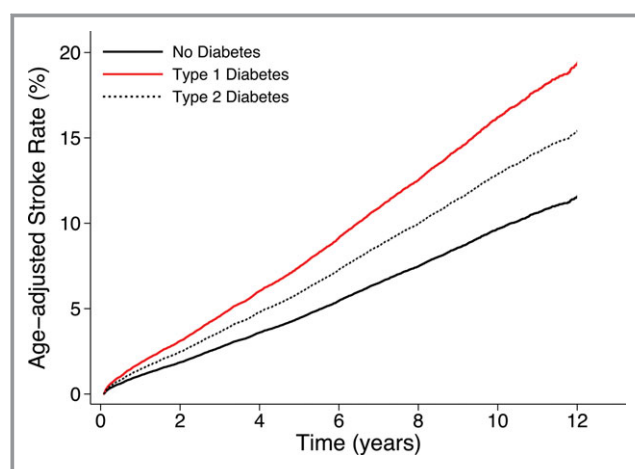


Figure. Age-adjusted stroke rate in 53 820 patients who underwent coronary artery bypass grafting in Sweden between 2000 and 2011 according to type of diabetes. The age-adjusted risk for stroke was significantly higher in patients with type 1 and type 2 diabetes compared with patients without diabetes.

Table 3. Long-Term Event Rates and Relative Risks for All-Cause Mortality or a Combination of Stroke and All-Cause Mortality in Patients Who Underwent Coronary Artery Bypass Surgery According to Diabetes Type

Outcome	Events/Person-Years	Incidence Rate Per 1000 Person-Years (95% CI)	Age-Adjusted Hazard Ratio (95% CI)	P Value	Multivariable Adjusted* Hazard Ratio (95% CI)	P Value
All-cause mortality						
No diabetes	9452/341 303	27.7 (27.1–28.3)	1.00 (Ref.)		1.00 (Ref.)	
Type 1 DM	155/5399	28.7 (24.5–33.6)	2.34 (1.99–2.75)	<0.001	1.98 (1.68–2.33)	<0.001
Type 2 DM	2130/74 875	28.4 (27.3–29.7)	1.10 (1.05–1.16)	<0.001	1.05 (1.00–1.10)	0.078
Stroke or death						
No diabetes	11 205/290 883	38.5 (37.8–39.2)	1.00 (Ref.)		1.00 (Ref.)	
Type 1 DM	184/4571	40.3 (34.8–46.5)	2.19 (1.89–2.54)	<0.001	1.86 (1.60–2.16)	<0.001
Type 2 DM	2661/62 738	42.4 (40.8–44.1)	1.18 (1.13–1.23)	<0.001	1.10 (1.06–1.15)	<0.001

DM indicates diabetes mellitus.

*Model included all variables reported in Table 1.

stroke was 1.59 (1.20–2.11) in type 1 diabetes, and 1.32 (1.23–1.43) in type 2 diabetes. The age-adjusted and multivariable-adjusted risks for the subtypes of stroke (ischemic and hemorrhagic) are shown in Table 2.

Long-Term Risk of All-Cause Mortality and the Combination of Stroke and All-Cause Mortality

During a mean follow-up time of 7.8 (SD 3.5) (median 7.7) years (421 576 person-years), in total, 22% (11 737 of

53 820) patients died of any cause: 22% (155 of 714) in type 1 diabetes, 21% (2130 of 10 054) in type 2 diabetes, and 22% (9452 of 43 052) in patients with no diabetes (Table 3). The crude incidence rates, and also the age-adjusted and multivariable-adjusted risks of all-cause mortality and the combination of stroke and all-cause mortality, respectively, are shown in Table 3. The multivariable adjusted risk for all-cause mortality, and also the combined outcome, was twice as high in patients with type 1 diabetes compared to patients without diabetes. The risk for these outcomes was only

Table 4. Duration and Treatment of Diabetes, and Glycemic Control in Patients With or Without Stroke

	Type 1 Diabetes			Type 2 Diabetes		
	No Stroke	Stroke	HR* (95% CI)	No Stroke	Stroke	HR* (95% CI)
DM duration, y, mean (SD)	41.8 (11.0)	41.5 (13.3)	1.01 (0.98–1.03)	8.47 (7.37)	9.10 (7.62)	1.01 (1.00–1.02)
Duration ≤10 years (Ref.)	0 (0%)	0 (0%)	—	6125 (67%)	596 (65%)	1.00
Duration >10 years	662 (100%)	52 (100%)	—	3014 (33%)	319 (35%)	1.11 (0.96–1.27)
Treatment						
Diet only (Ref.)	0 (0%)	0 (0%)	—	2189 (24%)	171 (19%)	1.00
Oral hypoglycemic agents	0 (0%)	0 (0%)	—	3928 (43%)	374 (41%)	1.13 (0.95–1.36)
Insulin with or without oral hypoglycemic agents	662 (100%)	52 (100%)	—	3022 (33%)	370 (40%)	1.23 (1.02–1.48)
HbA1c, mean (SD), %	8.44 (1.09)	8.46 (1.10)	0.93 (0.68–1.28)	7.41 (1.16)	7.61 (1.23)	1.07 (0.99–1.17)
HbA1c						
≤7.0% (Ref.)	55 (11%)	3 (8%)	1.00	1993 (44%)	142 (38%)	1.00
7.1% to 8.0%	134 (26%)	12 (32%)	1.63 (0.42–6.26)	1378 (30%)	117 (31%)	1.10 (0.86–1.42)
8.1% to 9.0%	200 (38%)	12 (32%)	1.12 (0.30–4.27)	757 (17%)	68 (18%)	1.04 (0.78–1.40)
9.1% to 10.0%	95 (18%)	6 (16%)	0.95 (0.22–4.15)	278 (6%)	35 (9%)	1.46 (0.99–2.13)
>10.0%	38 (7%)	5 (13%)	1.76 (0.33–9.26)	113 (3%)	13 (3%)	1.26 (0.71–2.26)

Data are shown as n (%) unless otherwise noted. DM indicates diabetes mellitus; HbA1c, glycosylated hemoglobin; HR, hazard ratio; Ref., reference category.

*Univariate hazard ratio.

slightly higher in patients with type 2 diabetes compared to patients without diabetes.

Importance of Duration, Treatment, and Glycemic Control

The univariate associations between duration of diabetes, treatment, and HbA1c, respectively, and all stroke is shown in Table 4. There was no significant association between HbA1c level and stroke in type 1 diabetes. However, it should be noted that the number of patients and strokes was low. There was no statistically significant association between duration of diabetes, or HbA1c levels, and stroke in type 2 diabetes. The risk of stroke was increased in patients treated with insulin compared to diet alone; the unadjusted hazard ratio was 1.23 (95% CI 1.02–1.48).

Discussion

In this long-term nationwide follow-up study of all patients who underwent CABG in Sweden during 12 years, we found that diabetes was associated with an increased risk of stroke compared with no diabetes. The increase in the risk of stroke was statistically significant in patients with both type 1 and type 2 diabetes after adjustment for clinically relevant baseline characteristics. Moreover, the risk of death in combination with stroke was doubled in patients with type 1 diabetes compared to those with no diabetes, and it was only slightly increased in patients with type 2 diabetes, compared to those with no diabetes.

Several previous studies have demonstrated that diabetes is an important risk factor for stroke.²⁰ Both type 1 and type 2 diabetes are associated with an increased absolute risk of stroke, although expected to be higher in type 2 diabetes, which mostly is explained by the fact that patients with type 2 diabetes are older. Not only age, but also sex can influence the risk of stroke in diabetes. Diabetes is associated with a higher relative risk of stroke in women than in men,²¹ particularly in type 1 diabetes.²² In recent studies where patients with diabetes have been divided into type 1 and type 2 diabetes, a rather high incidence rate of stroke have been demonstrated both in type 1 and type 2 diabetes.^{23,24} After separation of the diabetes types, an even further increased risk has been reported in type 1 diabetes.^{23,24} In our study, the association between type 1 and type 2 diabetes and risk of stroke was rather similar even if point estimates suggested a slightly stronger association between type 1 diabetes and risk of stroke. Also, it was recently demonstrated that type 1 diabetes individuals had a considerably higher risk for premature stroke compared with nondiabetic individuals.²⁵ Usually type 1 diabetes patients are at risk of stroke 10 to

15 years earlier than nondiabetes individuals; this risk is even higher in women.^{21,26} The excess risk, not only for stroke, but also all-cause mortality, and fatal and nonfatal CVD is greater in women than in men with type 1 diabetes.²² Besides differences in age and sex, chronic kidney disease and peripheral vascular disease were also more common in patients with type 1 diabetes compared to patients with type 2 diabetes in the present study. This may have contributed to the trend of a higher relative risk of stroke in the type 1 diabetes patients as compared with the relative risk in patients with type 2 diabetes. In contrast, the occurrence of atrial fibrillation was lower in type 1 diabetes patients.

We reported recently that patients with type 1 diabetes had more than a doubled long-term risk of death after CABG compared with patients without diabetes, whereas patients with type 2 diabetes had almost the same risk as patients without diabetes.¹⁵ Also in the current study, all-cause mortality was twice as high in type 1 diabetes patients compared to nondiabetes patients after multivariable adjustments for a number of potential risk factors. Interestingly, all-cause mortality, and the combined outcome (stroke and death), were only slightly increased in type 2 diabetes patients compared to patients without diabetes. Others have demonstrated an increased risk of death in type 1 diabetes patients.^{27,28} In a nationwide study, based on data from the Swedish National Diabetes Register, it was found that type 1 diabetes individuals, even at optimal glycemic control, had twice as high a risk of death, predominantly from CVD, compared to matched controls from the general population.²⁷ When myocardial infarction, stroke, and heart failure are reported as separate outcomes in individuals with diabetes, usually coronary heart disease is predominant.²⁹ In the present study, diabetes patients were more likely than nondiabetes patients to have a prior diagnosis of myocardial infarction or heart failure. In addition to the difference in age and sex, diabetes duration, chronic kidney disease, and peripheral artery disease were all more common in type 1 diabetes patients than in patients with type 2 diabetes. After multivariable adjustment, the hazard ratio for death only changed slightly, lending support to the idea that the pathophysiology underlying the excess risk of premature death in type 1 diabetes is still not well understood.²⁹

Diabetes causes earlier onset of atherosclerosis. Involvement of hyperglycemia, obesity, hyperlipidemia, hypertension, and insulin resistance are all well-known factors that all can induce and maintain atherosclerosis. Since we were not able to control for all these factors, we cannot exclude that there were differences between diabetes groups, or even between the nondiabetes group in terms of these risk factors. There were substantially more patients in the diabetes group compared to the nondiabetes group who were diagnosed with hypertension. This may, to some extent, explain the

increased risk of stroke observed in the diabetes group. In diabetes, hypertension has a stronger association with stroke than hyperglycemia has.^{30–32} Nevertheless, the association between hyperglycemia and increased risk of stroke has been demonstrated in some,³³ but not all studies² in diabetes individuals. Long-term studies in type 2 diabetes individuals comparing intensive versus standard glycemic control treatment have all failed to demonstrate a reduced risk of death and CVD (including fatal or nonfatal stroke).^{34–36} In one of these studies, the rate of death was even higher in the intensively treated group.³⁴ The reason for this remains unclear.³⁷ Moreover, there are differences in risk factors that are associated with an increased risk of ischemic stroke as compared to hemorrhagic stroke in diabetes. Hyperglycemia has a stronger association with ischemic than with hemorrhagic stroke.³³ When we categorized glucose control (by means of HbA1c), we found no association between glucose control and stroke. Even though the numbers of all stroke were large, it should be noted that the numbers after this categorization, especially in the type 1 diabetes group, were low. Moreover, after we subgrouped stroke (there were much fewer hemorrhagic strokes in all patient groups), the hazard ratio for hemorrhagic stroke was increased in the type 1 diabetes patients, although the total numbers were too few to make any firm interpretations of that observation. Some studies have shown an association between hyperglycemia and hemorrhagic stroke,³⁸ and other studies have not.³³ Our finding is consistent with other reports demonstrating a weak or even a lack of association between HbA1c levels and stroke in diabetes. Finally, we also found that the risk of stroke was increased in type 2 diabetes patients treated with insulin compared to diet alone. It has been debated whether insulin per se induces atherosclerosis. However, in the ORIGIN study, therapy with basal insulin glargine for more than 6 years had a neutral effect on CVD outcomes.³⁹ Therefore, it seems more likely that factors other than insulin may have confounded our observation (eg, type 2 diabetes patients treated with insulin are often older with longer diabetes duration and increased insulin resistance).

Strengths and Limitations

The main strength of the present study was the utilization of several high-quality national Swedish healthcare registers. We were able to classify all patients according to the type of diabetes, because we used the National Diabetes Register where all diabetes patients in Sweden are registered with virtually complete coverage. This allowed us to investigate the importance of type 1 and type 2 diabetes, respectively, for the risk of stroke. In addition we used the National Patient Register to retrieve information on strokes during follow-up. This register has complete coverage of Sweden since 1987,

and has been validated for a number of diagnoses including stroke.¹⁶ Furthermore, since the registers we used are virtually complete and nationwide, the risk of misclassification of disease or outcome was small, and there was no loss to follow-up. In addition, the level of health care provided to patients who undergo cardiac surgery in Sweden is comparable to the health care provided in the United States and other countries in Europe, which is why we believe that our results have a high external validity. To the best of our knowledge, this was the first study where the relation between subtypes of diabetes and risk of stroke was investigated in patients who underwent CABG.

As in every observational study, there may have been unmeasured risk factors that we could not adjust for in our statistical models. Even though our study population was large, there were few events when stroke was divided into subcategories (ischemic and hemorrhagic). Conclusions regarding the association between type of diabetes and subcategories of stroke must be drawn with caution. In addition, the point estimate suggested that the association between type 1 diabetes and stroke was stronger than the association between type 2 diabetes and stroke. However, even in this large study population, there were few events among patients with type 1 diabetes that led to confidence intervals being wide and overlapping. Our results cannot be generalized to the group of diabetes patients who undergo PCI. However, there is a general consensus that CABG is superior to PCI in patients with diabetes who are in need of multivessel revascularization, particularly in patients with more complex coronary artery disease.⁷ We had no information on medication with anticoagulants, which may ameliorate the risk of stroke, and may have influenced our results. Some of the patients without diabetes may in fact have had type 2 diabetes if tested, as shown in earlier studies.⁴⁰ However, it is likely that these patients had a shorter duration of diabetes and thus may have had a lower risk of stroke. Another limitation was that our findings were not generalizable to patients with prior cardiac surgery or a prior stroke because our study population included only patients who underwent primary CABG without a prior stroke. Due to study design, we were not able to estimate the stroke risk associated with diabetes and CABG separately. In order to do that, we would have needed access to a control group of patients who did not undergo CABG, which we did not have.

Conclusions

Diabetes patients, compared to nondiabetes patients, had an increased long-term risk of stroke after CABG that was independent of glycemic control and other cardiovascular risk factors. The risk of stroke was significantly higher in both type

1 and type 2 diabetes, compared to patients without diabetes. Moreover, the risk of death in combination with stroke was doubled in type 1 diabetes, whereas it was only slightly increased in patients with type 2 diabetes compared to patients without diabetes.

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Disclosures

None.

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