Twenty-Year Temporal Trends in Risk of Ischemic Stroke in Incident Type 2 Diabetes: A Danish Population-Based Cohort Study

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OBJECTIVE

We examined temporal trends in risk of first-time ischemic stroke in patients with incident type 2 diabetes mellitus (T2DM) and no prior atherosclerotic cardiovascular disease (ASCVD).

RESEARCH DESIGN AND METHODS

Using nationwide health registries, we identified all patients with incident T2DM without a prior hospital diagnosis of ASCVD from 1996 to 2015 in Denmark. Patients were assigned to 5-year periods based on the date of T2DM diagnosis and were followed for 5 years. Each patient was matched by sex and age with up to three individuals from the general population. Temporal trends in ischemic stroke were examined using Cox regression to compute hazard ratios (HRs). Temporal use of prophylactic cardiovascular medications was also assessed.

RESULTS

The study comprised 288,825 patients with incident T2DM and 782,232 general population individuals. From 1996–2000 to 2011–2015, the 5-year risk of first-time ischemic stroke was approximately halved in the T2DM cohort (5.2% vs. 2.7%; sex- and age-adjusted HR 0.52 [95% CI 0.49–0.55]). Patients diagnosed in 2011–2015 had increased risk of ischemic stroke compared with individuals in the general population; however, the risk difference narrowed over time (5.2% vs. 2.9% in 1996–1999 [difference 2.3%]; 2.7% vs. 2.0% in 2011–2015 [difference 0.7%]). Use of prophylactic cardiovascular medications increased markedly during the overall study period, especially use of statins (from 5% to 50%) and multiple antihypertensive drugs (from 18% to 33%).

CONCLUSIONS

From 1996 to 2015, the 5-year risk of first-time ischemic stroke was approximately halved in patients with incident T2DM and no prior ASCVD, coinciding with markedly increased use of prophylactic cardiovascular medications.

Type 2 diabetes mellitus (T2DM) and stroke are major global health challenges. They are among the leading causes of death and disability worldwide, and the prevalence of T2DM is reaching pandemic levels (1–3). T2DM is a major risk factor for ischemic stroke, and the combination of diabetes and atrial fibrillation increases the risk of ischemic stroke considerably (4–6).

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Several randomized trials targeting isolated or multiple risk factors support that multifactorial treatment of patients with T2DM prevents cardiovascular disease (7–13). Recently, we showed that patients with T2DM and no prior cardiovascular disease experienced major reductions in risk of myocardial infarction, cardiac death, and all-cause death in Denmark from 1996 to 2011 (14). Their risk reductions were much larger than those observed in the general population. Improvements in management of cardiovascular risk factors also are likely to have influenced the risk of ischemic stroke in patients with T2DM (6). Yet, few studies have examined temporal trends in incidence of ischemic stroke in patients with diabetes (15–20), and these studies had several limitations: restriction to patients with prevalent diabetes and cardiovascular disease (15–19), small sample size (20), or reliance on self-reported data (20). Moreover, although most studies found decreasing ischemic stroke incidence in patients with diabetes (16–19), some studies reported an increase in ischemic stroke incidence (15) or unchanged (20) incidence in this patient group during recent decades. Thus, temporal trends in risk of first-time ischemic stroke remain poorly understood in patients with incident T2DM and no prior atherosclerotic cardiovascular disease (ASCVD). In this population-based cohort study, we examined *1*) temporal trends in first-time ischemic stroke in patients with incident T2DM without prior ASCVD and in matched individuals from the general population, and *2*) temporal trends in use of prophylactic cardiovascular medications. We hypothesized that the risk of ischemic stroke decreased to a greater extent among patients with T2DM than among matched individuals, and that these trends temporally coincided with heightened use of prophylactic cardiovascular medications.

RESEARCH DESIGN AND METHODS

Study Design, Setting, and Data Sources

Our cohort study covered the entire population of Denmark and was based on national health registry data from 1996 to 2020. The Danish health care system provides universal tax-funded health care services to all Danish residents (21). The unique personal identifier assigned to all Danish residents at birth or upon immigration enables exact individual-level linkage and virtually complete follow-up (22). The following registries were used in the study: the Danish Civil Registration System, which has maintained records of date of birth, sex, and vital status (alive, dead, or emigrated) of all Danish residents since 1968; the Danish National Patient Registry (DNPR), which contains information on all inpatient stays since 1977 and on outpatient hospital clinic visits since 1995; and the Danish National Prescription Registry (NPR), which contains data on all prescriptions dispensed at Danish pharmacies since 1995 (22–24). For a subgroup analysis, we also used laboratory test results generated in general practice and hospital care registered in the Danish Clinical Laboratory Information System Database. Since 2005, this database has maintained full coverage of Northern Denmark (i.e., the North and Central Denmark regions, ~1.8 million persons, or 30% of the Danish population) (25,26).

Study Cohort

The DNPR and the NPR were used to identify all patients diagnosed with incident T2DM in Denmark between 1 January 1996 and 31 December 2015. Incident T2DM was defined as either *1*) first-time redemption of a glucose-lowering drug prescription, or *2*) first-time inpatient or outpatient hospital contact leading to a diabetes-related diagnosis. Codes and definitions are provided in Supplementary Table 1. A validation study of diabetes diagnoses provided a positive predictive value (PPV) of 95% for prescription-based diagnoses and 97% for hospital-based diagnoses (27). When both prescription data and hospital diagnoses were available, we used whichever occurred first to define the diabetes diagnosis date. Patients who had not resided in Denmark for at least 1 year prior to their diagnosis date were excluded. Supplementary Fig. 1 provides a flowchart of patient selection. Patients who redeemed an insulin prescription or had a hospital-based diagnosis before age 30 years or who redeemed a prescription for any glucose-lowering drug (s) before age 15 years were excluded due to the likelihood of type 1 diabetes. Female patients who gave birth within 9 months after a diabetes diagnosis were excluded because they likely had gestational diabetes. Patients with prior hospital-diagnosed polycystic ovary syndrome or who redeemed any biguanides prescription in combination with clomiphene within 12 months after diabetes diagnosis were excluded because they were likely to have polycystic ovary syndrome. We further excluded patients with prior hospital-diagnosed ASCVD, defined as prior diagnoses of ischemic stroke, transient ischemic attack, myocardial infarction, and/or peripheral artery disease (including peripheral revascularization and lower-limb amputation). Patients with prior percutaneous coronary intervention or coronary artery bypass grafting were also excluded.

On the date of diabetes diagnosis, each patient was matched by sex and age with up to three individuals (exact ratio 1:2.7) from the general population who had no prior record of diabetes. The general population cohort was randomly selected through the Danish Civil Registration System and was sampled with replacement (28). Matched individuals were excluded if they had not resided in Denmark for at least 1 year prior to the inclusion date or if they had prior diagnoses of ASCVD.

Comorbidity and Medication

Comorbidities were identified in the DNPR using codes from the ICD-8 and ICD-10. Redeemed prescriptions were ascertained from the NPR. Baseline medical treatment was defined as redemption of one or more prescription(s) within 12 months prior to (or on) the inclusion date. Treatment with prophylactic cardiovascular medications after study inclusion was defined as redemption of one or more prescription(s) within 12 months after the inclusion date. Codes and definitions are provided in Supplementary Table 1. In an interaction analysis between T2DM and atrial fibrillation on the risk of ischemic stroke, we examined patients with or without atrial fibrillation diagnosis at baseline. ICD-10 code I48 was used to define atrial fibrillation, although this code also covers atrial flutter. However, atrial fibrillation and atrial flutter are both associated with an increased risk of ischemic stroke. Furthermore, approximately 95% of all I48 codes correspond to atrial fibrillation and only 5% to atrial flutter (23).

Outcome

Information on first-time ischemic stroke was obtained from the DNPR on the basis

of discharge diagnoses from an inpatient hospital admission (Supplementary Table 1). We used the ICD-10 code I63 (ischemic stroke) together with I64 (unspecified stroke) to define ischemic stroke. This additional code increased the sensitivity of ischemic stroke identification because approximately two-thirds of unspecified stroke cases in the DNPR are ischemic strokes (23). In a validation study, the diagnosis of ischemic stroke has a high PPV of 97% (23).

Statistical Analyses

Follow-up began on the diabetes diagnosis date and continued until an outcome, death, emigration, or a maximum of 5 years of follow-up. The last patient concluded follow-up on 31 December 2020. On the basis of the T2DM diagnosis (inclusion) date, patients with diabetes and matched individuals from the general population were stratified by calendar period in 5 year intervals: 1996–2000, 2001–2005, 2006–2010, and 2011–2015. Five-year cumulative incidence proportions were computed. A competing-risk model was used to estimate the cumulative incidence of ischemic stroke accounting for the competing risk of death. Cox regression analysis was used to compute 5 year hazard ratios (HRs) for ischemic stroke among *1*) patients with T2DM by calendar period, using patients diagnosed in 1996–2000 as reference; and *2*) patients with T2DM versus matched individuals, by stratifying on matched sets and using matched individuals from the same calendar period as the reference. In the first analysis, comparing patients with T2DM by calendar period, HRs were adjusted for sex and age (using restricted cubic splines with seven knots). The proportional hazards assumption was verified by visual inspection of log-log plots and by Schoenfeld residuals, and no violations were found. Robust variance estimators were applied. If matched individuals developed T2DM during follow-up (5%), they were not censored from the general population cohort. This decision was made from a clinical perspective (i.e., to state the risk of adverse events between a patient with incident T2DM and an individual with the same age and sex but no diabetes at that time).

The interaction effect of T2DM and atrial fibrillation on the risk of ischemic stroke was examined by calculating interaction contrasts (29). The interaction contrast is a measure of the ischemic stroke risk in addition to what can be explained by the baseline risk of ischemic stroke among individuals without T2DM and atrial fibrillation, and the separate effects of T2DM and atrial fibrillation on the risk of ischemic stroke on an additive scale. We repeated Cox regression analyses for individuals with or without T2DM stratified by atrial fibrillation at baseline, using patients without T2DM and atrial fibrillation as the reference.

We performed three additional analyses. First, we stratified analyses of patients with T2DM by sex and age category ($<$60 years, 60–69 years, 70–79 years, and $\geq$80 years). Second, we repeated the analysis of outcomes in patients with T2DM versus matched individuals, where individuals were eligible for inclusion in the general population cohort until their diabetes diagnosis date, at which point they were censored and entered the diabetes population. Third, we performed a sensitivity analysis with any type of stroke as an outcome. All analyses were performed using Stata/MP version 14.0.

Ethical Considerations

The study was reported to the Danish Data Protection Agency. According to Danish law, strictly registry-based studies do not require ethical approval or informed consent from participants.

RESULTS

A total of 288,825 patients with incident T2DM and 782,232 individuals from the general population were included in the study. The number of patients with incident T2DM increased from 52,463 in 1996–2000 to 83,243 in 2011–2015. During follow-up, 22 patients (0.01%) with diabetes and 106 matched individuals (0.01%) were lost to follow-up and were censored on the day of loss to follow-up.

Baseline Characteristics

Baseline characteristics of the diabetes and the general population cohorts are presented in Table 1 and Supplementary Table 2. Median age at diabetes diagnosis was 62 years in 1996–2000 and 61 years in 2011–2015. For both cohorts, prevalence of all comorbidities except heart failure increased incrementally during the study period. The proportion of patients redeeming prescriptions for insulin and sulfonylureas decreased over time, whereas the frequency of prescriptions for biguanides increased.

In a subcohort of patients from Northern Denmark with incident T2DM, the median prediagnosis HbA_{1c} level decreased from 9.2% (77 mmol/mol) in the earliest study period to 6.9% (52 mmol/mol) in the latest study period, and the median prediagnosis LDL cholesterol level decreased from 3.6 mmol/L to 2.9 mmol/L (Supplementary Table 3). The median postdiagnosis HbA_{1c} and LDL cholesterol levels also decreased gradually during the study period. The median prediagnosis and postdiagnosis levels of the estimated glomerular filtration rate declined as well during the study period. The use or registration of measurements of HbA_{1c} levels, LDL cholesterol levels, and estimated glomerular filtration rates changed considerably over the study period (Supplementary Table 3).

Temporal Trends in Ischemic Stroke Incidence

Between 1996–2000 and 2011–2015, the 5-year risk of first-time ischemic stroke measured as the cumulative incidence was nearly halved in patients with incident T2DM (5.2% [95% CI 5.0–5.4] vs. 2.7% [95% CI 2.6–2.8]) (Fig. 1). On a relative scale, the HR of ischemic stroke also was approximately halved (crude HR 0.48 [95% CI 0.46–0.51]; sex- and age-adjusted HR [aHR] 0.52 [95% CI 0.49–0.55]) (Table 2). Patients with diabetes remained at increased risk of ischemic stroke compared with the matched individuals at the end of the study period, but the risk difference narrowed over time (5-year risk difference: 2.3% [95% CI 2.1–2.5] in 1996–2000 vs. 0.7% [95% CI 0.6–0.8] in 2011–2015) (Table 2).

Interaction Between T2DM and Atrial Fibrillation on the Risk of Ischemic Stroke

Supplementary Table 4 shows the interaction between T2DM and atrial fibrillation on the risk of ischemic stroke. The 5-year risk of ischemic stroke was highest in patients with combined T2DM and atrial fibrillation (7.7% [95% CI 7.1–8.3]) and lowest in those with neither T2DM nor atrial fibrillation (2.2% [95% CI 2.2–2.2]). With a reservation of statistical uncertainty, the interaction contrast indicated a potential synergistic interaction between T2DM and atrial fibrillation on

Table 1—Baseline characteristics of patients with incident T2DM and matched individuals from the general population

	Patients with T2DM, by year interval				All patients with diabetes	All matched individuals from the general population
	1996–2000	2001–2005	2006–2010	2011–2015		
Participants, *n*	52,463	67,693	85,426	83,243	288,825	782,232
Male sex	28,228 (53.8)	35,289 (52.1)	43,208 (50.6)	43,037 (51.7)	149,762 (51.9)	397,930 (50.9)
Age, median (Q_1–Q_3), years	62 (51–72)	60 (50–71)	60 (49–69)	61 (50–70)	61 (50–70)	59 (49–69)
Age group, years						
<40	4,224 (8.1)	7,185 (10.6)	11,421 (13.4)	9,584 (11.5)	32,414 (11.2)	96,748 (12.4)
40–49	7,176 (13.7)	9,208 (13.6)	11,966 (14.0)	11,822 (14.2)	40,172 (13.9)	118,288 (15.1)
50–59	13,010 (24.8)	16,985 (25.1)	19,132 (22.4)	19,007 (22.8)	68,134 (23.6)	192,874 (24.7)
60–69	12,330 (23.5)	16,580 (24.5)	22,918 (26.8)	22,717 (27.3)	74,545 (25.8)	198,860 (25.4)
70–79	10,327 (19.7)	11,456 (16.9)	13,496 (15.8)	13,961 (16.8)	49,240 (17.0)	120,466 (15.4)
≥80	5,396 (10.3)	6,279 (9.3)	6,493 (7.6)	6,152 (7.4)	24,320 (8.4)	54,996 (7.0)
Comorbidities						
Hypertension*	20,976 (40.0)	32,351 (47.8)	46,746 (54.7)	47,027 (56.5)	147,100 (50.9)	189,106 (24.2)
COPD	3,693 (7.0)	5,608 (8.3)	7,281 (8.5)	8,223 (9.9)	24,805 (8.6)	36,818 (4.7)
Heart failure	2,519 (4.8)	3,000 (4.4)	3,040 (3.6)	2,764 (3.3)	11,323 (3.9)	9,072 (1.2)
Atrial fibrillation	2,555 (4.9)	3,750 (5.5)	4,892 (5.7)	5,456 (6.6)	16,653 (5.8)	19,322 (2.5)
Moderate-to-severe renal disease	693 (1.3)	1,089 (1.6)	1,456 (1.7)	1,937 (2.3)	5,175 (1.8)	6,099 (0.8)
Moderate-to-severe liver disease	231 (0.4)	411 (0.6)	523 (0.6)	581 (0.7)	1,746 (0.6)	1,367 (0.2)
Connective tissue disease	1,537 (2.9)	2,020 (3.0)	2,699 (3.2)	3,129 (3.8)	9,385 (3.2)	17,496 (2.2)
Any malignancy	4,299 (8.2)	5,907 (8.7)	8,067 (9.4)	9,362 (11.2)	27,635 (9.6)	55,960 (7.2)
Hyperthyroidism	921 (1.8)	1,386 (2.0)	1,716 (2.0)	1,853 (2.2)	5,876 (2.0)	11,156 (1.4)
Heart valve disease	511 (1.0)	781 (1.2)	1,231 (1.4)	1,461 (1.8)	3,984 (1.4)	6,842 (0.9)
Prior venous thromboembolism	1,096 (2.1)	1,598 (2.4)	2,232 (2.6)	2,629 (3.2)	7,555 (2.6)	11,483 (1.5)
Smoking (proxy)†	7,509 (14.3)	9,977 (14.7)	12,952 (15.2)	14,270 (17.1)	44,708 (15.5)	73,459 (9.4)
Hospital-diagnosed obesity	3,519 (6.7)	5,383 (8.0)	8,006 (9.4)	9,323 (11.2)	26,231 (9.1)	15,011 (1.9)
Alcoholism-related disorders	2,410 (4.6)	3,489 (5.2)	4,434 (5.2)	4,643 (5.6)	14,976 (5.2)	19,358 (2.5)
Medications						
Insulin	982 (1.9)	735 (1.1)	1,007 (1.2)	1,181 (1.4)	3,905 (1.4)	0 (0)
Biguanides	4,827 (9.2)	21,790 (32.2)	52,865 (61.9)	64,037 (76.9)	143,519 (49.7)	0 (0)
Sulfonylureas	25,174 (48.0)	19,827 (29.3)	8,980 (10.5)	1,133 (1.4)	55,114 (19.1)	0 (0)
DPP4i	0 (0)	0 (0)	359 (0.4)	665 (0.8)	1,024 (0.4)	0 (0)
GLP-1 analogs	0 (0)	0 (0)	93 (0.1)	434 (0.5)	527 (0.2)	0 (0)
SGLT-2 inhibitors	0 (0)	0 (0)	0 (0)	48 (0.1)	48 (0)	0 (0)
Statins	1,203 (2.3)	9,351 (13.8)	29,579 (34.6)	32,014 (38.5)	72,147 (25.0)	56,088 (7.2)
High-intensity statins	<5 (0)	284 (0.4)	1,207 (1.4)	3,600 (4.3)	5,096 (1.8)	3,419 (0.4)
Other lipid-lowering drugs	0 (0)	<5 (0)	281 (0.3)	451 (0.5)	736 (0.3)	744 (0.1)
Beta-blockers	6,260 (11.9)	10,883 (16.1)	15,453 (18.1)	14,959 (18.0)	47,555 (16.5)	58,934 (7.5)
ACE inhibitor/ARBs	7,886 (15.0)	17,571 (26.0)	31,667 (37.1)	33,792 (40.6)	90,916 (31.5)	95,908 (12.3)
Calcium channel blockers	7,167 (13.7)	9,581 (14.2)	15,599 (18.3)	17,312 (20.8)	49,659 (17.2)	63,457 (8.1)
Thiazides	8,425 (16.1)	13,091 (19.3)	16,683 (19.5)	13,682 (16.4)	51,881 (18.0)	68,616 (8.8)
Aspirin	6,010 (11.5)	10,807 (16.0)	16,777 (19.6)	12,033 (14.5)	45,627 (15.8)	53,392 (6.8)
ADP receptor inhibitors	7 (0)	52 (0.1)	154 (0.2)	538 (0.6)	751 (0.3)	1,164 (0.1)
Vitamin K antagonist	1,261 (2.4)	2,283 (3.4)	3,679 (4.3)	3,949 (4.7)	11,172 (3.9)	12,890 (1.6)
DOACs	0 (0)	0 (0)	14 (0)	451 (0.5)	465 (0.2)	670 (0.1)

Data are presented as *n* (%) unless otherwise indicated. ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; DPP4i, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide-1; Q, quartile; SGLT-2, sodium-glucose cotransporter 2. *Hypertension was defined as ICD-10 or ICD-8 diagnosis codes for hypertension and/or redemption of one or more prescriptions for antihypertensive treatment. †Smoking (proxy) was defined by ICD-10 or ICD-8 diagnosis codes for chronic bronchitis, emphysema, and COPD, and medications used to treat COPD.

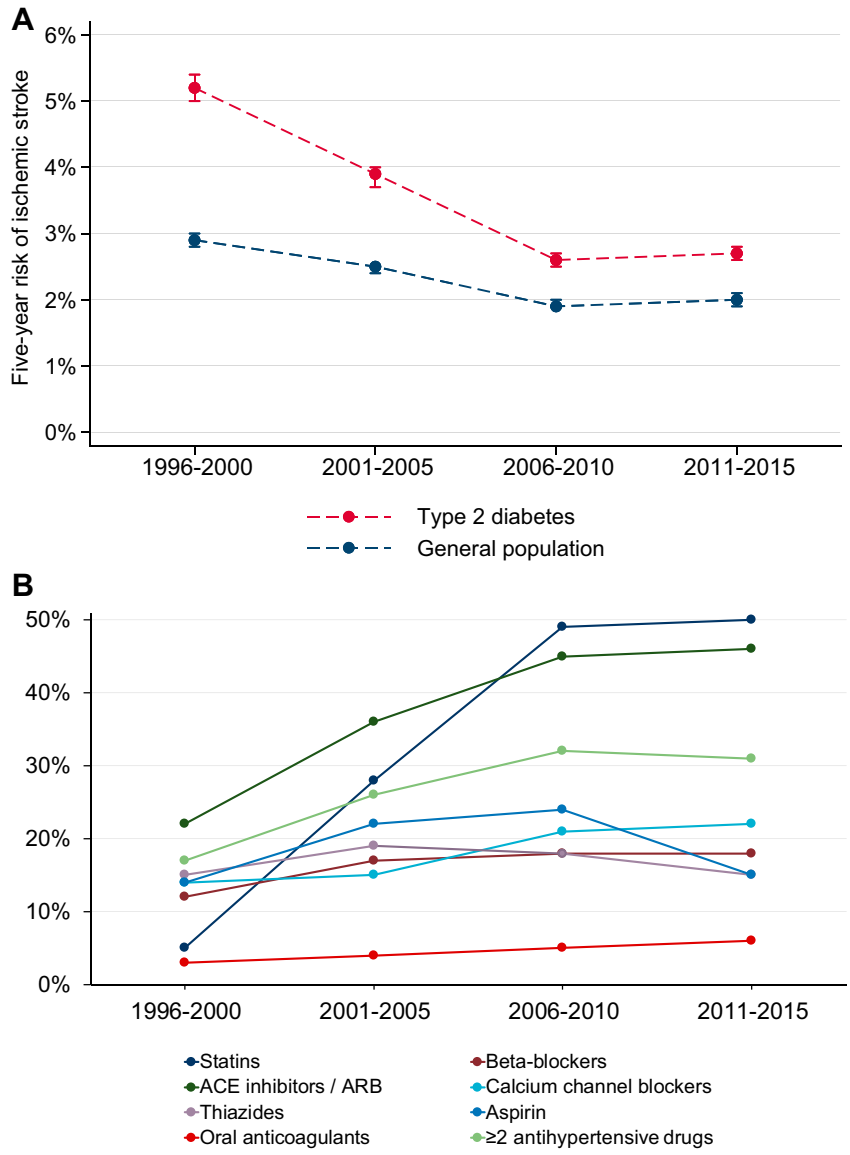

Figure 1—Five-year risk of ischemic stroke in patients with incident T2DM and matched individuals from the general population, all without prior ASCVD (*A*); and corresponding time trends in use of cardiovascular medications within 12 months after T2DM diagnosis (*B*). ARB, angiotensin receptor blocker.

the risk of ischemic stroke (0.4 [95% CI −0.3, 1.1]). Among patients with combined T2DM and atrial fibrillation, the aHR was amplified (2.44 [95% CI 2.25–2.64]) compared with patients with T2DM alone (aHR 1.53 [95% CI 1.49–1.57]), patients with atrial fibrillation alone (aHR 1.76 [95% CI 1.63–1.91]), and patients without T2DM and atrial fibrillation (reference).

Prophylactic Cardiovascular Medications

Use of prophylactic cardiovascular medications within 12 months after a T2DM diagnosis increased markedly over time (Fig. 1 and Supplementary Table 5). From the earliest to the latest calendar period, use of the following drugs especially increased: statins (from 5 to 50%), ACE inhibitors/angiotensin II receptor blockers (from 22 to 47%), calcium channel blockers (from 15 to 23%), and multiple antihypertensive drugs (from 18 to 33%). Use of aspirin increased gradually from the first to the third calendar period (16% in 1996–2000; 26% in 2006–2010) and then decreased to 16% in 2011–2015. Use of oral anticoagulants among patients with combined T2DM and atrial fibrillation increased remarkably during the study period (from 35 to 58%).

Additional Analyses

In the analysis of patients with incident T2DM by calendar period, age and sex did not seem to modify the results, except for patients aged ≥80 years who were at increased risk of ischemic stroke (HR 0.65 [95% CI 0.57–0.74]) in the latest calendar period compared with the entire study period (Supplementary Table 6). Censoring matched individuals developing T2DM during follow-up did not alter the risk estimates of patients with T2DM versus matched individuals (Supplementary Table 7). Including any type of stroke as an outcome yielded results comparable to those in the main analyses (Supplementary Table 8).

CONCLUSIONS

In this Danish nationwide cohort study from 1996 to 2015, the 5 year incidence of first-time ischemic stroke was approximately halved, from 5.2 to 2.7%, in patients with incident T2DM without prior ASCVD. In the matched general population comparison cohort, the corresponding percentages were 2.9% and 2.0%. Thus, the risk difference between patients with incident T2DM and matched individuals in the general population narrowed from 2.3% in the earliest study period (1996–2000) to only 0.7% % in the latest study period (2011–2015). These temporal improvements were mirrored by increased use of prophylactic cardiovascular medications, especially use of statins and multiple antihypertensive drugs.

The observed ischemic stroke reductions most likely reflect a combination of medical advances. First, our data suggest that we have improved prophylactic cardiovascular treatment of patients with incident T2DM. For a subgroup of patients, we furthermore observed decreasing LDL cholesterol and HbA_{1c} levels. These findings are consistent with those of prior, landmark randomized clinical trials showing the importance of blood glucose control, blood pressure control, statin use, and multifactorial intervention in reducing cardiovascular risk in patients with T2DM (7–12). In addition, we report the new, important, and valid observation that ischemic stroke incidence was halved in a nationwide cohort. The link between stroke-risk reduction and optimized prophylactic cardiovascular treatment is concordant with

Table 2—Five-year risk of ischemic stroke in patients with incident T2DM and matched individuals from the general population

	T2DM				General population		T2DM vs. general population
	Individuals (events), *n*	5-Year cumulative incidence* (95% CI), %	Crude HR (95% CI)	Adjusted HR† (95% CI)	Individuals (events), *n*	5-Year cumulative incidence* (95% CI), %	Sex- and age-matched HR‡ (95% CI)
1996–2000	52,463 (2,730)	5.2 (5.0–5.4)	Reference	Reference	143,339 (4,121)	2.9 (2.8–3.0)	1.95 (1.87–2.03)
2001–2005	67,693 (2,622)	3.9 (3.7–4.0)	0.73 (0.69–0.77)	0.77 (0.73–0.81)	183,444 (4,510)	2.5 (2.4–2.5)	1.65 (1.58–1.72)
2006–2010	85,426 (2,193)	2.6 (2.5–2.7)	0.47 (0.45–0.50)	0.53 (0.50–0.56)	230,994 (4,397)	1.9 (1.9–2.0)	1.35 (1.30–1.42)
2011–2015	83,243 (2,056)	2.7 (2.6–2.8)	0.48 (0.46–0.51)	0.52 (0.49–0.55)	224,455 (4,052)	2.0 (1.9–2.1)	1.39 (1.33–1.46)

*Accounting for the competing risk of death. †Comparing patients with T2DM by calendar period, adjusted for sex and age. ‡Comparing patients with T2DM with matched individuals from the same calendar period as the reference.

a recent Swedish cohort study, which demonstrated that patients with T2DM who had five risk factors (elevated HbA_{1c}, elevated LDL cholesterol, albuminuria, smoking, and elevated blood pressure) within target ranges had little or no excess risk of death, myocardial infarction, or stroke, compared with the general population (30).

Second, increasing awareness of, and screening for, diabetes may have contributed to the observed risk reduction, potentially leading to earlier diabetes diagnosis and earlier initiation of prophylactic treatment. Hence, the median age at diabetes diagnosis decreased slightly from 62 years to 61 years during the study period. We also observed a large increase in the incidence of diabetes during the study period. These findings most likely reflect a combination of a true increased incidence of T2DM as well as increased screening. Third, advances in patient education and self-management behaviors including smoking cessation and physical activity have likely played a role, too.

Our findings in this cohort of patients with incident T2DM are generally consistent with trends in incidence of ischemic stroke in patients with prevalent diabetes and cardiovascular disease observed in Sweden, Scotland, the U.S., and South Korea (16–19). However, a Spanish nationwide cohort study reported a modest increase in the incidence rates of ischemic stroke hospitalizations in patients with T2DM between 2003 and 2012 (adjusted incidence rate ratio 1.02 [95% CI 1.01–1.03]) (15). This discrepancy might be partly explained by differences in patient cohorts. The Spanish study examined patients with prevalent T2DM who were older (mean age 71–72 years) and had more comorbidities (e.g., 15–32% had atrial fibrillation). Importantly, the authors could not distinguish first ischemic stroke event from subsequent ischemic stroke events if readmission occurred after 30 days and, hence, did not exclusively examine first-time ischemic stroke. A recent cross-sectional study of U.S. adults with newly diagnosed T2DM (within 2 years) reported increased control of risk factors such as glycemic level and blood pressure but no difference in self-reported history of stroke from 1988–1994 to 2011–2018 (6.8% vs. 6.4%) (20). However, the study was limited by its cross-sectional design (lack of temporality), self-reported data on exposure and outcome (possible misclassification), and a small sample size (n = 1,486), and, therefore, limited precision in the temporal outcome estimates.

Atrial fibrillation is an important risk factor for stroke (6). Several studies have shown that the combination of diabetes and atrial fibrillation increases the risk of ischemic stroke considerably (4–6). We had expected a more pronounced synergistic interaction (i.e., the joint effect of diabetes and atrial fibrillation is higher than the effect expected by the sum of their individual effects) between T2DM and atrial fibrillation on the risk of ischemic stroke. It should be noted that the prevalence of atrial fibrillation might be underreported in patients with T2DM. Thus, previous studies have shown both that undiagnosed silent atrial fibrillation is common (~10%) in patients with T2DM and that these subclinical episodes are associated with an increased risk of stroke (31,32). If atrial fibrillation was underreported among patients with T2DM, this could have attenuated the observed joint effect of T2DM and atrial fibrillation and thus the measured synergistic interaction.

Use of prophylactic cardiovascular medications increased markedly during the study period, most likely reflecting changing guidelines and increased focus on the importance of preventive treatment. Unlike most of the prophylactic medications we examined, aspirin use within 12 months after T2DM diagnosis decreased in the latest study period. This finding may reflect the debated use of aspirin for primary prevention of ASCVD, because of possible lack of net benefit given an increased bleeding risk (33,34). Accordingly, Danish guidelines have changed during the study period to more cautious recommendations for aspirin use as primary prevention in patients with T2DM (Supplementary Table 9).

Despite substantial improvements in ischemic stroke incidence in patients with incident T2DM, we still observed that these patients were at increased risk of ischemic stroke compared with the general population. Interestingly, the risk of ischemic stroke was similar in the two latest study periods. Likewise, use of most prophylactic medications after T2DM diagnosis stagnated in the two latest study periods. Thus, in the last study period, only 50% of patients with T2DM received statins, and ~60% of patients with combined diabetes and atrial fibrillation received oral

anticoagulant treatment. These results indicate a potential for further reductions of stroke incidence in patients with T2DM. Moreover, antidiabetic drugs such as glucagon-like peptide-1 analogs and sodium-glucose cotransporter 2 inhibitors have been associated with a reduced risk of stroke in patients with diabetes. Wider use of these drugs hopefully will lead to further reductions in stroke incidence (35–37). The observed stagnation in stroke risk may also be explained by a different risk profile of the diabetes population (e.g., more obesity) or a shift in the population diagnosed with T2DM after the 2012 introduction of HbA_{1c}, which may have removed some patients with low cardiovascular risk from the pool of incident T2DM (38).

Strengths of our study include use of nationwide population-based registries in a tax-supported, public health care system with virtually complete follow-up, which minimizes the risk of selection bias (21). Moreover, previous validation studies have found high PPV of the codes used to identify the diabetes population and the study outcomes (23,27).

Our study has several limitations. We lacked information on socioeconomic status and lifestyle changes such as eating habits, physical activity, and smoking. However, we used surrogate measures of smoking, although survey data from the Danish National Health Survey indicate that the proportion of daily smokers has decreased substantially over time in Denmark (39% in 1994, 34% in 2000, 30% in 2005, 21% in 2010, and 17% in 2017) (39). Moreover, although the PPV of the obesity discharge diagnosis is high, this diagnosis remains underreported (40). We observed that almost all examined comorbidities increased incrementally in both patients with diabetes and matched individuals. This finding might reflect, at least partially, detection bias or surveillance bias as well as improved registration of diagnoses in the health registries during the study period. Another concern is that the proportion of missing data for laboratory test results was high in the beginning of the study period, which could, in part, reflect selection bias: prior to 2012 and the widespread use of HbA_{1c} to diagnose diabetes, HbA_{1c} measurements were restricted mainly to hospitalized patients with glycemic control problems. Finally, the causal relation between the observed decreased risk of ischemic stroke and increased use of prophylactic medications is based on findings from previous randomized clinical trials (7–12). Our temporal trends analyses only indirectly indicate that these guideline-directed changes led to major reductions in stroke incidence among patients with T2DM.

In conclusion, the risk of ischemic stroke was halved in patients with incident T2DM and no prior ASCVD from 1996 to 2015 in Denmark. Use of guideline-directed, well-documented prophylactic cardiovascular medications increased markedly during the study period, which likely contributed to the observed risk reductions.

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