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ORIGINAL RESEARCH

Association of Diabetes Duration and Glycemic Control With Stroke Rate in Patients With Atrial Fibrillation and Diabetes: A Population-Based Cohort Study

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BACKGROUND: There are limited data on the association of diabetes duration and glycemic control with stroke risk in atrial fibrillation (AF). Our objective was to study the association of diabetes duration and glycated hemoglobin (HbA1c) with the rate of stroke in people with diabetes and newly diagnosed AF.

METHODS AND RESULTS: This was a population-based cohort study using linked administrative data sets. We studied 37 209 individuals aged ≥66 years diagnosed with AF in Ontario between April 2009 and March 2019, who had diabetes diagnosed 1 to 16 years beforehand. The primary outcome was hospitalization for stroke at 1 year. Cause-specific hazard regression was used to model the association of diabetes duration and glycated hemoglobin (HbA1c) with the rate of stroke. Restricted cubic spline analyses showed increasing hazard ratios (HR) for stroke with longer diabetes duration that plateaued after 10 years and increasing HRs for stroke with HbA1c levels >7%. Relative to patients with <5 years diabetes duration, stroke rates were significantly higher for patients with ≥10 years duration (HR, 1.45; 95% CI, 1.16–1.82; *P*=0.001), while diabetes duration 5 to <10 years was not significantly different. Relative to glycated hemoglobin 6% to <7%, values ≥8% were associated with higher stroke rates (HR, 1.44; 95% CI, 1.12–1.84; *P*=0.004), while other HbA1c categories were not significantly different.

CONCLUSIONS: Longer diabetes duration and higher glycated hemoglobin were associated with significantly higher stroke rates in patients with AF and diabetes. Models for stroke risk prediction and preventive care in AF may be improved by considering patients' diabetes characteristics.

Key Words: atrial fibrillation ■ diabetes ■ diabetes duration ■ glycated hemoglobin ■ stroke

Individuals with diabetes are at increased risk of atrial fibrillation (AF), making diabetes a common comorbidity at AF diagnosis.[1,2] The $CHADS_2$ and CHA_2DS_2VASc risk scores are predicated on the premise that risk of stroke in AF increases in the presence of additional stroke risk factors, including diabetes.[3] Clinical practice guidelines[3–6] recommend anticoagulation for most patients with co-existing AF and diabetes since their stroke risk is perceived to be high enough to offset the bleeding risk from anticoagulation. These approaches treat diabetes as a binary entity with equivalent weight to other risk factors and do not account for substantial heterogeneity among people with diabetes related to disease duration, glycemic control, microvascular complications, or treatment with anti-hyperglycemic agents.

There are marked differences between patients treated with diabetes today and their counterparts

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CLINICAL PERSPECTIVE

What Is New?

- Patients with atrial fibrillation and diabetes whose diabetes duration was <5 years have ≈45% lower stroke rates than patients with diabetes of >10 years' duration.
- Patients with atrial fibrillation and diabetes who have normal glycated hemoglobin levels have ≈44% lower stroke rates than patients with glycated hemoglobin >8%.

What Are the Clinical Implications?

- We can improve models for stroke risk prediction and strategies for risk reduction in atrial fibrillation by considering patients' diabetes-specific characteristics.
- Higher stroke rates in people with longer diabetes duration and worse glycemic control highlights the need for control of vascular risk factors to reduce their contribution to stroke risk.

Nonstandard Abbreviations and Acronyms

$CHADS_2$	congestive heart failure, hypertension, age ≥75, diabetes, stroke (doubled)
CHA_2DS_2VASc	congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74, sex category

from many years ago who were used to derive the approaches currently used to estimate stroke risk in AF.[3,6] Since recent guidelines advocate for diabetes screening in patients at increased cardiovascular risk,[7,8] we are increasingly detecting earlier and milder forms of diabetes.[9,10] Furthermore, novel treatment options for diabetes make it increasingly feasible to achieve good glycemic control with lower risk of hypoglycemia.[11] This makes it important to re-evaluate how the risk of stroke in patients with co-existing AF and diabetes varies based on their diabetes-specific characteristics. We conducted a population-based retrospective cohort study to evaluate the association of diabetes duration (years since diagnosis) and glycemic control, as measured by glycated hemoglobin (HbA1c), with the rate of stroke in patients with AF. We hypothesized that the rate of stroke in patients with AF and diabetes increases with longer diabetes duration and higher HbA1c.

METHODS

Data Sources

Ontario's residents receive universal health coverage through the Ontario Health Insurance Plan. This allows for administrative data sets to be linked using unique encoded identifiers and analyzed at ICES.[12] The Canadian Institute for Health Information Discharge Abstract Database records data on hospitalized patients and the National Ambulatory Care Reporting System collects data on emergency departmen visits. Physician billing claims are recorded in the Ontario Health Insurance Plan database. The Ontario Laboratories Information System database contains information on laboratory test results, including HbA1c and creatinine.[13] The Registered Persons Database maintains vital statistics, including date of death. Prescription medication coverage is provided for people aged >65 years through the Ontario Drug Benefit program.[14] The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act,[15] which does not require review by a research ethics board. The paper is reported following the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement. While data sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS.

Cohort Creation

We created a cohort of community-dwelling individuals (ie, not residing in long-term care facilities) who were newly diagnosed with AF in Ontario between April 2009 and March 2019, and who had a diagnosis of diabetes >1 year before AF diagnosis. We used a validated algorithm to identify patients with AF based on hospital or emergency department discharge records, or the presence of 4 physician billing claims within 365 days for AF. This algorithm has a specificity of 99.1% (95% CI, 98.9%–99.3%).[16] The index date was that of first documentation of AF. Diabetes was identified using the Ontario Diabetes Database.[17] Patients were included if they had 3 physician billings claims for diabetes within 365 days; this algorithm has a specificity of 99.1% (95% CI, 99.0%–99.1%).[18]

Diabetes duration was defined as the time between the dates of AF diagnosis and first physician billing claim for diabetes. We excluded individuals whose diabetes was first recognized <1 year before AF diagnosis as they may have had longer-lasting AF or diabetes that was first recognized during a period of increased health care contact surrounding the diagnosis of either illness. We also excluded patients whose diabetes was diagnosed before 1992 since they are not reliably

captured by the Ontario Diabetes Database. Thus, the longest possible diabetes duration for patients diagnosed with AF in 2009 was 16 years. Accordingly, we excluded patients with diabetes duration >16 years to allow comparison of diabetes duration across different years of cohort entry. We further excluded individuals aged <66 years (medication data not reliably available), those with valvular disease, and those without HbA1c or creatinine measurements within 365 days before AF diagnosis.

Exposure and Outcome Variables

The key exposures were diabetes duration and glycemic control before AF diagnosis. Glycemic control was estimated using a single HbA1c level measured within 365 days before AF diagnosis, or 30 days after AF diagnosis for patients without measurements in the prior year. We categorized diabetes medications at AF diagnosis as insulin or oral hypoglycemic agents (glucagon-like peptide-1 receptor agonists were not available on the ODB before 2019). As a marker of microvascular diabetic nephropathy, we studied estimated glomerular filtration rate, estimated from creatinine levels using the Chronic Kidney Disease Epidemiology Collaboration equation.[19] We used the HbA1c and creatinine values closest to the AF diagnosis date.

The primary outcome was hospitalization for stroke using *International Classification of Diseases, Tenth Revision (ICD-10)* codes I60, I61, I63 (excluding I63.6), I64, and H34.1, which were validated to have 82% sensitivity.[20] The primary outcome definition included hemorrhagic strokes since these are usually caused by transformation of ischemic strokes.[21,22] Extradural and subdural bleeds (intracranial bleeds outside the brain) were excluded from the primary outcome. We limited follow-up to 1 year since patients frequently acquire additional stroke risk factors over time[23] and to maintain consistency with the seminal $CHADS_2$[6] and $CHADS_2$-VASc[3] studies. The date of last follow-up was March 31, 2020.

Statistical Analysis

Data were summarized using the median (with interquartile range) and/or mean (with SD) for continuous variables and counts (with percentages) for categorical variables. We categorized patients based on clinically relevant categories for diabetes duration (<5 years, 5 to <10 years, ≥10 years) and baseline HbA1c (<6%, 6% to <7%, 7% to <8%, ≥8). Baseline characteristics were compared between these categories using ANOVA or the Chi-square test as appropriate.

We modeled time to stroke using cause-specific hazard regression models where diabetes duration and HbA1c were represented using restricted cubic spline functions[24,25] to study their association with the rate of stroke without forcing the relationship to be linear. The analysis utilized 5 knots set at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles. We used the entire cohort to develop the model, then used the fitted model to estimate the hazard ratio (HR) of stroke at each value of diabetes duration and HbA1c. The HR was estimated relative to the values of diabetes duration of 1-year and HbA1c 6%, which were associated with the lowest adjusted hazard of stroke. We truncated the presented figures at HbA1c <5%, HbA1c >15%, and diabetes duration >15 years given small numbers of individuals and events at these extremes.

After review of restricted cubic spline analyses, we maintained the initial categorization of diabetes duration and HbA1c that had been based on clinical considerations. To present data more intuitively to clinicians, we used cause-specific hazard regression to quantify the association of stroke rate with diabetes duration and HbA1c as categorical variables. Since we hypothesized that there may be different patterns of association between patient characteristics and the rate of stroke in patients with new onset versus long-standing diabetes, we repeated this analysis after stratifying the cohort based on the diabetes duration categories. We conducted similar analyses which stratified patients by HbA1c category. We also conducted 3 sensitivity analyses to verify the stability of observed associations between diabetes duration and HbA1c with the rate of stroke. First, we limited the analysis to patients who were not anticoagulated at the index date. The second sensitivity analysis was limited to patients aged <75 years who have a lower risk of stroke and the competing risk of death. The third model limited the outcome to ischemic strokes (ie, excluded hemorrhagic strokes).

Most regression models adjusted for statins, angiotensin antagonists, and $CHADS_2$-VASc[3] risk factors on the index date: age, sex, heart failure (HF), hypertension, stroke, or transient ischemic attack, and vascular disease (defined as a composite of coronary or peripheral vascular disease); the stratifying variable was omitted from the models used for stratified analyses. We also adjusted for anticoagulation use as a time-varying covariate. Patients were censored if they were event-free at 1 year and death was treated as a competing risk. Analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC). Statistical significance was defined as a two-tailed *P*-value <0.05. Dr Abdel-Qadir had full access to all the data in the study and takes responsibility for its integrity and data analysis.

RESULTS

Cohort Characteristics

As shown in Figure S1, we identified 66 769 community-dwelling individuals aged ≥66 years with

newly diagnosed AF and prevalent diabetes, of whom 37 209 individuals met study inclusion criteria. Their baseline characteristics are listed in Table 1. Although HbA1c and diabetes duration were correlated, there was substantial overlap between all diabetes duration and HbA1c categories. Individuals with longer diabetes duration were older and were more likely to have cardiovascular and non-cardiovascular comorbidities. The median time between the most recent HbA1c test and the index date was 64 (interquartile range, 21–135) days, with 36 291 (97.5%) of HbA1c measurements taken before AF diagnosis. Higher HbA1c was associated with younger age but longer diabetes duration. Further baseline characteristics by HbA1c category are provided in Table S1.

Crude Outcomes

Over the 365 days following AF diagnosis, there were 5480 (14.7%) deaths and 601 (1.6%) strokes (532 ischemic). A total of 22 507 (60.5%) individuals were dispensed prescriptions for anticoagulation during that year with a median time to anticoagulation of 23 (interquartile range, 5–84) days among those not anticoagulated at baseline. The crude 1-year risks of death and stroke after stratification by diabetes duration and HbA1c categories are summarized in Table S2. The crude risk of stroke was higher among individuals with longer diabetes duration and higher HbA1c. The crude risk of death also increased with longer diabetes duration, HbA1c <6% and HbA1c ≥8%.

Independent Association of Diabetes Duration and HbA1c With Stroke Rate

As illustrated in Figure 1, the restricted cubic spline analyses demonstrated there was an increase in the HR for stroke with longer diabetes duration, but this plateaued after 10 years. In contrast, Figure 2 shows that HbA1c levels >7% were associated with a nearly linear increase in the HR for stroke. There was a non-significant trend towards higher rates of stroke among individuals with the lowest HbA1c levels.

Table 1. Baseline Characteristics of the Cohort, Stratified by Diabetes Duration

Variable	Total n=37 209	1 to <5 y n=9204	5 to <10 y n=13 753	≥10 y n=14 252	*P* value
Diabetes duration in y, median (IQR)	8 (5–12)	3 (2–4)	8 (6–9)	13 (11–14)	<0.001
Diabetes duration in y, mean ± SD	8.5 (4.1)	3.1 (1.2)	7.5 (1.4)	12.9 (1.7)	<0.001
HbA1c value, median (IQR)	7 (6–7)	7 (6–7)	7 (6–7)	7 (6–8)	<0.001
HbA1c value, mean ± SD	6.9 (1.1)	6.7 (1.0)	6.8 (1.1)	7.1 (1.2)	<0.001
HbA1c <6%, n (%)	6053 (16.3%)	1673 (18.2%)	2422 (17.6%)	1958 (13.7%)	<0.001
HbA1c 6% to <7%, n (%)	17 800 (47.8%)	5132 (55.8%)	6762 (49.2%)	5906 (41.4%)	
HbA1c 7% to <8%, n (%)	8624 (23.2%)	1684 (18.3%)	3078 (22.4%)	3862 (27.1%)	
HbA1c ≥8%, n (%)	4732 (12.7%)	715 (7.8%)	1491 (10.8%)	2526 (17.7%)	
Age, y, median (IQR)	77 (72–83)	76 (71–82)	77 (72–83)	77 (72–83)	<0.001
Female sex, n (%)	15 633 (42.0%)	3894 (42.3%)	5763 (41.9%)	5976 (41.9%)	0.8
Heart failure, n (%)	12 566 (33.8%)	2794 (30.4%)	4539 (33.0%)	5233 (36.7%)	<0.001
Hypertension, n (%)	34 228 (92.0%)	8245 (89.6%)	12 727 (92.5%)	13 256 (93.0%)	<0.001
Ischemic stroke or transient ischemic attack, n (%)	1352 (3.6%)	306 (3.3%)	495 (3.6%)	551 (3.9%)	0.09
Ischemic heart disease, n (%)	13 834 (37.2%)	3471 (37.7%)	4978 (36.2%)	5385 (37.8%)	0.01
Peripheral vascular disease, n (%)	792 (2.1%)	198 (2.2%)	294 (2.1%)	300 (2.1%)	0.97
CHA_2DS_2VASc score; median (IQR)	5 (4–6)	5 (4–5)	5 (4–5)	5 (4–6)	<0.001
CHA_2DS_2VASc score; mean (SD)	4.8 (1.2)	4.7 (1.2)	4.7 (1.2)	4.8 (1.2)	<0.001
Estimated glomerular filtration rate (mL/min per 1.73 m^2), median (IQR)	64 (47–80)	66 (50–81)	64 (48–81)	61 (43–79)	<0.001
Oral hypoglycemics, n (%)	26 356 (70.8%)	5395 (58.6%)	9397 (68.3%)	11 564 (81.1%)	<0.001
Insulin, n (%)	4977 (13.4%)	548 (6.0%)	1354 (9.8%)	3075 (21.6%)	<0.001
Statins, n (%)	28 843 (77.5%)	6916 (75.1%)	10 743 (78.1%)	11 184 (78.5%)	<0.001
Angiotensin antagonists, n (%)	29 185 (78.4%)	6897 (74.9%)	10 791 (78.5%)	11 497 (80.7%)	<0.001
Anticoagulation, n (%)	13 382 (36.0%)	3381 (36.7%)	4998 (36.3%)	5003 (35.1%)	0.02
Warfarin, n (%)	7366 (19.8%)	1952 (21.2%)	2729 (19.8%)	2685 (18.8%)	<0.001
Direct oral anticoagulant, n (%)	6054 (16.3%)	1431 (15.5%)	2291 (16.7%)	2332 (16.4%)	0.08

HbA1c indicates glycated hemoglobin, and IQR, interquartile range.

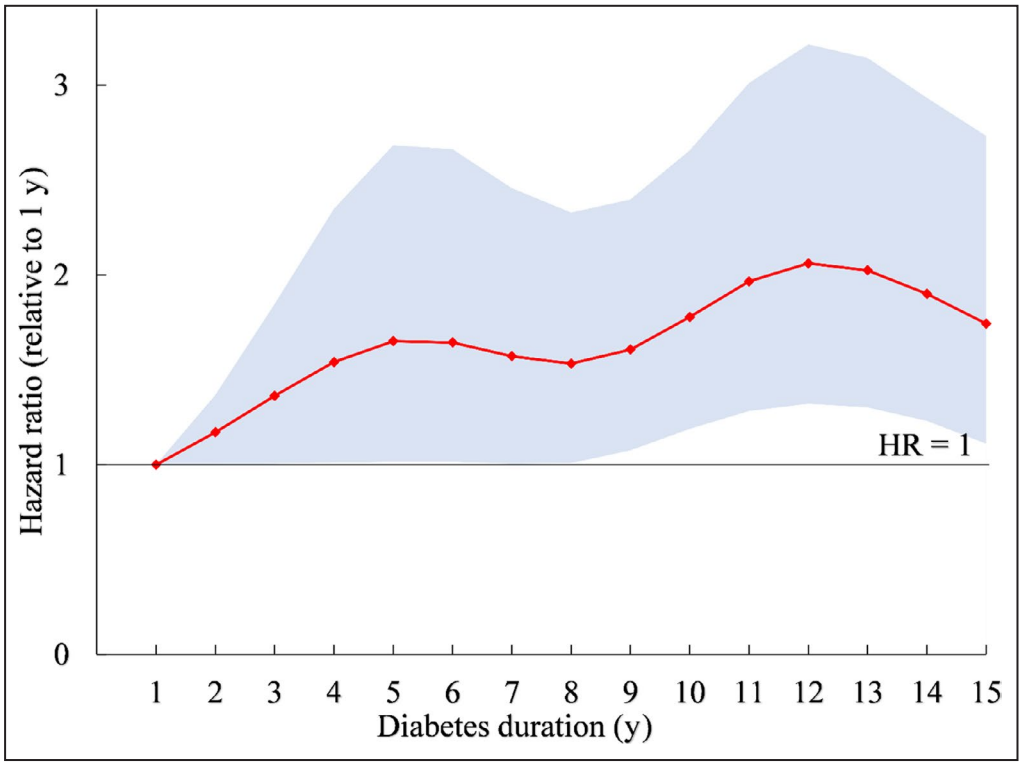

Figure 1. Restricted cubic spline analysis of the relationship between diabetes duration and the rate of stroke (adjusted for glycated hemoglobin, age, sex, heart failure, hypertension, stroke/transient ischemic attack, vascular disease, anticoagulant use [time-varying], insulin, oral hypoglycemics, statins, and estimated glomerular filtration rate).
HR indicates hazard ratio.

The regression model examining the association of stroke with categories of diabetes duration and HbA1c is summarized in Table 2. Relative to <5 years diabetes duration, the stroke rate was significantly higher with ≥10 years duration (HR, 1.45; 95% CI, 1.16–1.82; *P*=0.001); while diabetes duration 5 to <10 years was not significantly different from <5 years (HR, 1.20; 95% CI, 0.95–1.50; *P*=0.12). Relative to HbA1c 6% to <7%, values ≥8% were associated with higher stroke rates (HR, 1.44; 95% CI, 1.12–1.84; *P*=0.004), while other HbA1c categories were not significantly different. Diabetes medications, angiotensin antagonists, and estimated glomerular filtration rate were not independently associated with stroke rate. Statins were associated with significantly lower stroke rate (HR, 0.68; 95% CI, 0.57–0.82; *P*<0.001).

The stratified analyses by diabetes duration categories did not reveal important deviations in the association of most patient characteristics with the stroke rate (see Table S3). One exception was the association of the lowest HbA1c category (<6%) with the rate of stroke (see Figure 3). Among individuals with diabetes of <5 years' duration, this lowest HbA1c category was associated with the lowest stroke rate relative to HbA1c 6% to <7% (HR, 0.47; 95% CI, 0.25–0.89; *P*=0.02). In patients with longer diabetes duration categories, the point estimate of the HR for HbA1c <6% exceeded 1. When analyses were stratified by HbA1c categories, the association of diabetes duration with stroke rate was most prominent for patients with HbA1c <6%. In contrast, diabetes duration did not correlate with stroke rate in patients with HbA1c ≥8% (see Table S4). The sensitivity analyses (summarized in Tables S5 and S6) revealed comparable trends to the primary analysis for the association of diabetes duration with stroke in patients who were not anticoagulated at baseline, those aged <75 years, and when the outcome was limited to ischemic strokes.

DISCUSSION

In this population-based cohort study of individuals with newly diagnosed AF and pre-existing diabetes (>1 year), we observed that longer diabetes duration, and higher baseline HbA1c were associated with higher stroke rates. In stratified analyses by diabetes duration, we observed that the lowest HbA1c category (<6%) was associated with lower stroke rates in patients with recent-onset diabetes (<5 years), but not among those with longer diabetes duration. The use of insulin, oral

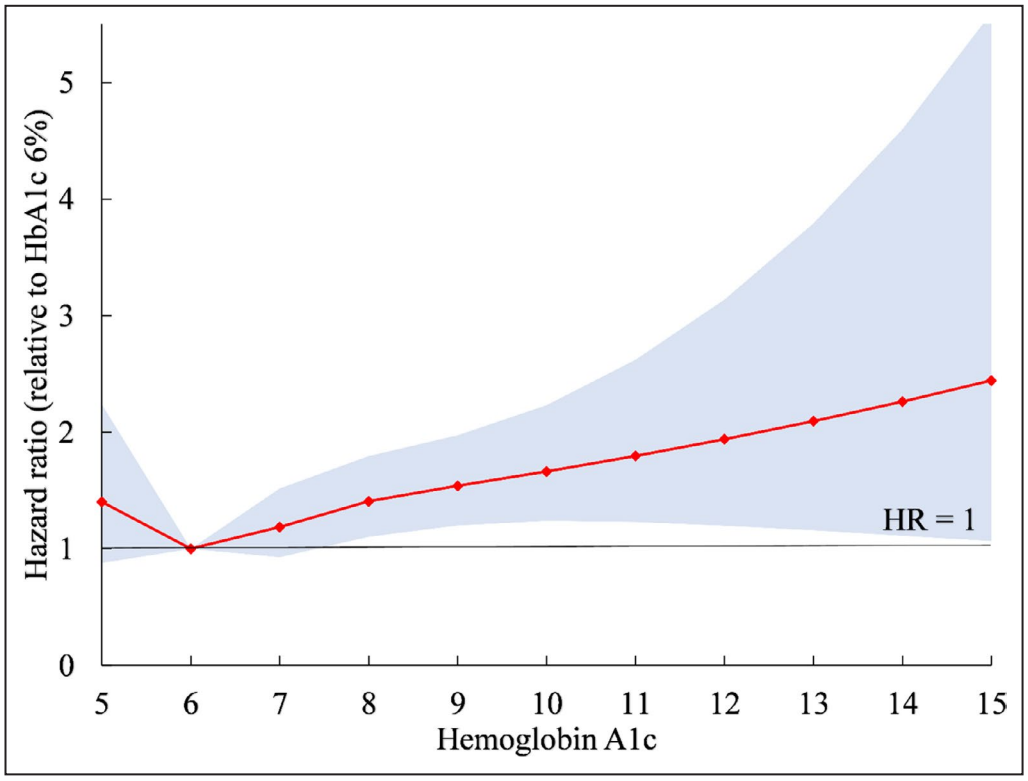

Figure 2. Restricted cubic spline analysis of the relationship between glycemic control, as measured by glycated hemoglobin, and the rate of stroke (adjusted for diabetes duration, age, sex, heart failure, hypertension, stroke/transient ischemic attack, vascular disease, anticoagulant use [time-varying], insulin, oral hypoglycemics, statins, and estimated glomerular filtration rate). HbA1c indicates glycated hemoglobin; and HR, hazard ratio.

hypoglycemics, and estimated glomerular filtration rate was not significantly associated with the rate of stroke.

Our study reinforces the heterogeneity of stroke risk in patients with AF and diabetes that was reported in prior research. A study of patients recruited between 1996 and 2003[26] reported that diabetes duration ≥3 years was associated with higher rates of ischemic stroke compared with duration <3 years (adjusted HR, 1.74; 95% CI, 1.10–2.76). Another study of patients hospitalized between 2000 and 2011[27] reported that diabetes duration ≥15 years was associated with higher stroke rates compared with 0 to 4 years (HR, 1.48; 95% CI, 1.29–1.70). These studies' inclusion criteria limit applicability to contemporary patients whose diabetes and AF are diagnosed earlier and treated better, mostly out of hospital.

The association of HbA1c with stroke or thromboembolism in patients with AF has been less consistent in previous studies. In the aforementioned study of patients diagnosed with AF before 2003, HbA1c was not associated with the rate of ischemic stroke.[26] Conversely, 3 other studies concluded that the rate of stroke or thromboembolism increases with HbA1c[28–30] in a linear manner. The inconsistency with our findings may relate to accrual dates of prior studies, which do not reflect contemporary treatments. Moreover, the lowest HbA1c category was <6.4% in 1 study[29] and <6.5% in another,[28] while the third was not limited to patients with diabetes.[30] Thus, they were not designed to examine the impact of tight glycemic control, which is associated with higher mortality in elderly individuals with diabetes.[31,32] We observed a higher incidence of death but similar incidence of stroke among patients with HbA1c <6% relative to 6% to <7%. However, HbA1c <6% was associated with lower rates of stroke in the subgroup of patients with <5 years of diabetes; this subgroup of recent-onset diabetes was not specifically described in prior studies.

There are fewer data on the relationship between diabetes medications and stroke risk that are specific to patients with AF. One study reported that only insulin-requiring patients with diabetes had higher risk of thromboembolism compared with patients without diabetes.[33] Another study reported a gradient of increasing stroke risk from patients without diabetes, to diabetes not requiring insulin, with highest risk in patients requiring insulin.[34] However, these studies did not account for both diabetes duration and glycemic control.

Our observation of higher stroke rates with longer diabetes duration and higher HbA1c levels were in a

Table 2. Results of the Multivariable Regression Model Assessing the Relationship of Patient Characteristics With the Rate of Stroke

	Hazard ratio	95% CI	*P* value
Diabetes duration (relative to 1 to <5 y)	…	…	…
5 y to <10 y	1.20	0.95–1.50	0.12
≥10 y	1.45	1.16–1.82	0.001
HbA1c category (relative to 6% to <7%)	…	…	…
<6%	0.97	0.76–1.24	0.81
7% to <8%	1.08	0.88–1.33	0.47
≥8%	1.44	1.12–1.84	0.004
Age (per y)	1.03	1.02–1.04	<0.001
Female sex	1.23	1.04–1.44	0.01
Heart failure	1.08	0.90–1.28	0.40
Hypertension	1.30	0.92–1.84	0.14
Stroke or transient ischemic attack	2.73	2.07–3.61	<0.001
Vascular disease	1.04	0.88–1.24	0.65
Oral hypoglycemics	1.12	0.93–1.35	0.23
Insulin	0.82	0.63–1.08	0.16
Estimated glomerular filtration rate per 10 mL/min per 1.73 m^2	0.99	0.95–1.03	0.60
Anticoagulant use (time-varying)	0.67	0.57–0.80	<0.001
Statins	0.68	0.57–0.82	<0.001
Angiotensin antagonists	0.87	0.72–1.07	0.18

HbA1c indicates glycated hemoglobin; and IQR, interquartile range.

largely anticoagulated cohort. This suggests that these higher-risk patients may benefit from further interventions to reduce their stroke risk, including blood pressure and lipid control. Our stratified analyses did not suggest that anticoagulation had less efficacy in patients with longer diabetes duration or higher HbA1c. Thus, the increased risk may reflect higher baseline event rates and contributions from non-cardioembolic strokes. This dovetails with our observation that statins were associated with reductions in stroke rate comparable with those from anticoagulation. Consideration should also be given to preferential use of metformin[35] and glucagon-like peptide-1 receptor agonists,[36–40] since they reduce the risk of stroke in all-comers with diabetes, and avoidance of sulfonylureas given their association with higher stroke risk.[41] Conversely, dipeptidyl peptidase-4 inhibitors[37–40,42,43] and sodium-glucose transport protein 2 inhibitors[37–40,44–48] seem neutral with regards to stroke risk in all-comers with diabetes. However, it is unknown if these associations extend to patients with concomitant diabetes and AF.

Our data also suggest that our current approaches to stroke risk prediction may be improved by considering diabetes duration and HbA1c in patients with AF. The American College of Cardiology/American Heart Association and European Society of Cardiology guidelines[3–6] recommend that patients with AF and diabetes, but without other stroke risk factors, should be considered for anticoagulation but provide minimal guidance about how the decision should be made. Our observation of lower stroke rates in patients with recent-onset and well-controlled diabetes raise the possibility that this subset of diabetes may not warrant a point on the $CHADS_2$-VA_2Sc score. Conversely, longer diabetes duration and higher HbA1c may each warrant a point on a revised score. Accordingly, greater consideration may need to be given to anticoagulating patients with longer durations of diabetes or poor glycemic control, even if they do not have other risk factors. Conversely, anticoagulation may be considered less strongly in patients with newer-onset and well-controlled diabetes. However, we cannot make these conclusions from this study since we analyzed the rate of stroke (rather than absolute incidence) and did not include comparisons to patients with AF who do not have diabetes. This hypothesis should be pursued in future studies in a lower risk group of patients with AF and diabetes.

This study has several limitations. The administrative data sets used in this study did not contain data on blood pressure, body mass index, and smoking, while lipid data were missing for a large group of patients. Thus, we could not account for those important factors. Furthermore, we could not differentiate atherosclerotic from embolic strokes. Our analysis relied on a single HbA1c value at baseline, which can fluctuate over time. Our findings cannot be applied to long-term care residents. The algorithm for identifying outpatients with AF introduces an immortal time bias (patients fulfilling criteria must not have died before the fourth claim) and may limit generalizability to patients with AF with less health system contact. Baseline characteristics were identified using algorithms that prioritize specificity over sensitivity, which may lead to the under-detection of comorbidities in patients with newer-onset diabetes (because of less overall health system contact). However, this would bias us towards the null hypothesis as we would overestimate the rate of stroke in patients with recent-onset diabetes if we did not adjust for such comorbidities.

CONCLUSIONS

Among individuals with newly diagnosed AF and prevalent diabetes, longer duration of diabetes, and higher HbA1c were associated with higher rates of stroke. This suggests that current models for stroke risk prediction in AF and strategies for risk reduction can be improved by incorporating these diabetes-specific characteristics in decision-making. Future studies should evaluate if there are important differences

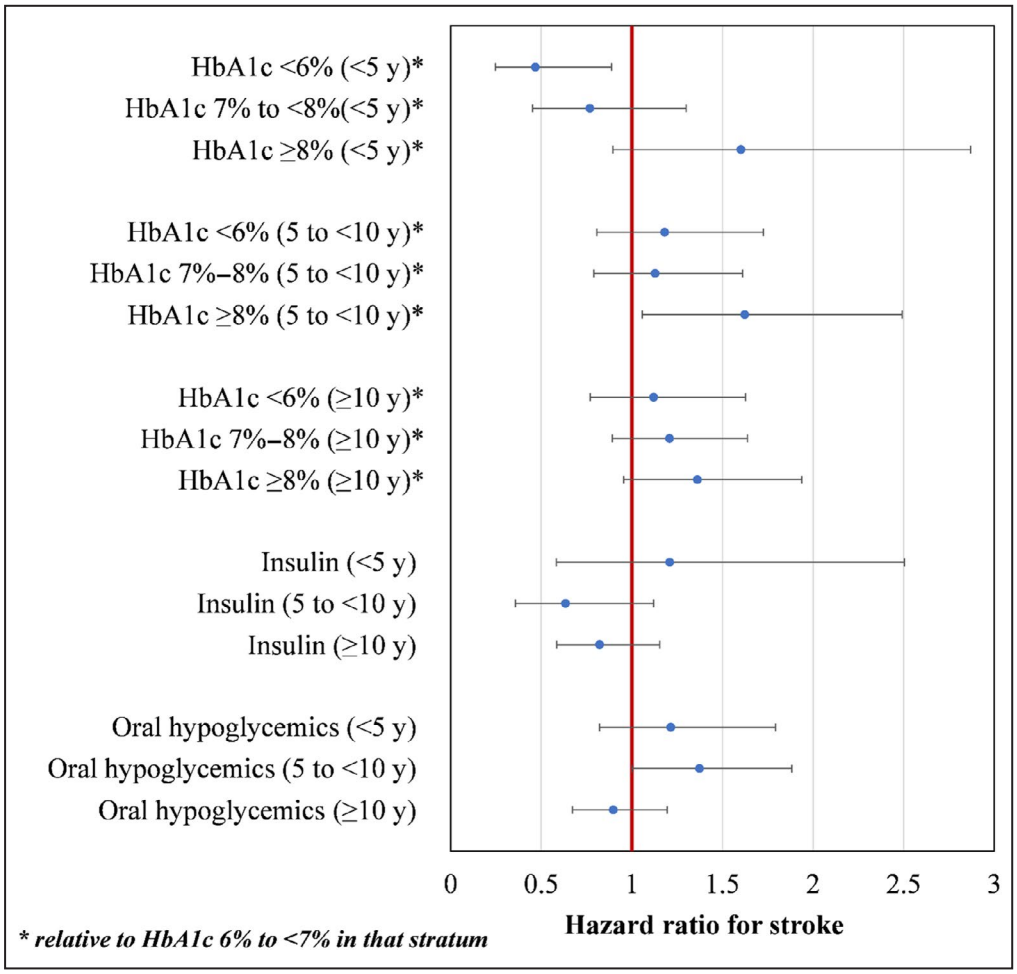

Figure 3. Summary of the stratified analysis examining the association of glycated hemoglobin, oral hypoglycemics, and insulin with the rate of stroke.
Patients were stratified by diabetes duration into recent-onset (1 to <5 years), moderate duration (5 to <10 years) and long-standing diabetes duration (≥10 years) categories. HbA1c indicates glycated hemoglobin; and HR, hazard ratio.

in stroke incidence between patients with AF and recent-onset, well-controlled diabetes, and those without diabetes.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S6
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics of the cohort by HbA1c category.

Variable	<6%	6% to <7%	7 to <8%	≥8%	p-value
	n=6,053	n=17,800	n=8,624	n=4,732	
HbA1c value; median (IQR)	6 (6-6)	6 (6-7)	7 (7-8)	9 (8-10)	<.001
HbA1c value; mean ± SD	5.6 (0.3)	6.4 (0.3)	7.4 (0.3)	9.1 (1.2)	<.001
Diabetes duration in years; median (IQR)	8 (5-11)	8 (5-11)	9 (6-13)	10 (7-13)	<.001
Diabetes Duration in years; mean ± SD	7.9 (4.0)	7.9 (4.1)	9.1 (4.1)	9.9 (4.0)	<.001
Age; median (IQR)	78 (72-84)	78 (72-83)	76 (71-82)	75 (70-81)	<.001
Female sex, n(%)	2,570 (42.5%)	7,779 (43.7%)	3,461 (40.1%)	1,823 (38.5%)	<.001
Hypertension, n(%)	5,612 (92.7%)	16,475 (92.6%)	7,868 (91.2%)	4,273 (90.3%)	<.001
Heart failure, n(%)	2,052 (33.9%)	5,683 (31.9%)	2,975 (34.5%)	1,856 (39.2%)	<.001
Ischemic heart disease, n(%)	2,057 (34.0%)	6,466 (36.3%)	3,379 (39.2%)	1,932 (40.8%)	<.001
Peripheral vascular disease, n(%)	154 (2.5%)	367 (2.1%)	169 (2.0%)	102 (2.2%)	0.09
Stroke or transient ischemic attack, n(%)	219 (3.6%)	602 (3.4%)	310 (3.6%)	221 (4.7%)	<.001
CHA_2DS_2VASc score; median (IQR)	5 (4-6)	5 (4-6)	5 (4-5)	5 (4-6)	<.001
CHA_2DS_2VASc score; mean (SD)	4.8 (1.2)	4.8 (1.1)	4.7 (1.2)	4.7 (1.2)	0.002
Estimated glomerular filtration rate, median (IQR)	64 (46-80)	64 (48-80)	63 (47-80)	63 (45-80)	0.13
Oral hypoglycemics, n(%)	2,631 (43.5%)	11,705 (65.8%)	7,583 (87.9%)	4,437 (93.8%)	<.001
Insulin, n(%)	225 (3.7%)	1,262 (7.1%)	1,624 (18.8%)	1,866 (39.4%)	<.001
Statins, n(%)	4,195 (69.3%)	13,981 (78.5%)	6,977 (80.9%)	3,690 (78.0%)	<.001
Angiotensin antagonists, n(%)	4,353 (71.9%)	14,085 (79.1%)	7,045 (81.7%)	3,702 (78.2%)	<.001
Anticoagulation, n(%)	2,063 (34.1%)	6,511 (36.6%)	3,167 (36.7%)	1,641 (34.7%)	<.001
Warfarin, n(%)	849 (14.0%)	3,084 (17.3%)	1,538 (17.8%)	767 (16.2%)	<.001
DOAC, n(%)	1,080 (17.8%)	2,894 (16.3%)	1,387 (16.1%)	693 (14.6%)	<.001

Table S2. Crude outcomes by Diabetes Duration and HbA1c at one year.

Category	Death (any cause)	Stroke (ischemic or hemorrhagic)
Diabetes duration categories		
1 to <5 years	1,157 (12.6%)	117 (1.3%)
5 to < 10 years	1,976 (14.4%)	212 (1.5%)
≥10 years	2,347 (16.5%)	272 (1.9%)
HbA1c categories		
<6%	1,053 (17.4%)	91 (1.5%)
6% to <7%	2,421 (13.6%)	270 (1.5%)
7% to <8%	1,221 (14.2%)	140 (1.6%)
≥8%	785 (16.6%)	100 (2.1%)

Table S3. **Regression models analyzing the relationship between patient characteristics and the rate of stroke, after stratification by diabetes duration.**

	Duration 1 to <5 years			**Duration 5 to <10 years**			**Duration ≥ 10 years**		
Variable	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
HbA1c <6%*	0.47	0.25-0.89	0.02	1.18	0.81-1.73	0.39	1.12	0.77-1.63	0.55
HbA1c 7% to <8%*	0.77	0.45-1.30	0.32	1.13	0.79-1.61	0.51	1.21	0.89-1.64	0.22
HbA1c ≥8*	1.60	0.89-2.87	0.11	1.62	1.06-2.49	0.03	1.36	0.96-1.94	0.09
Age (per year)	1.04	1.01-1.07	0.004	1.04	1.02-1.06	<.001	1.02	1.00-1.04	0.01
Female sex	1.29	0.89-1.88	0.17	1.23	0.94-1.62	0.14	1.20	0.94-1.53	0.14
Hypertension	1.12	0.59-2.15	0.73	1.42	0.76-2.65	0.27	1.33	0.77-2.31	0.31
Heart failure	0.99	0.65-1.49	0.95	1.35	1.01-1.80	0.04	0.91	0.70-1.19	0.49
Vascular disease	0.97	0.65-1.43	0.86	0.91	0.68-1.22	0.53	1.18	0.92-1.52	0.19
Stroke or transient ischemic attack	2.61	1.31-5.19	0.006	2.63	1.64-4.22	<.001	2.93	1.96-4.37	<.001
eGFR (per 10ml/min/1.73m2)	0.95	0.86-1.04	0.28	1.02	0.95-1.09	0.61	0.99	0.93-1.05	0.65
Oral hypoglycemics	1.21	0.82-1.79	0.33	1.37	1.00-1.88	0.05	0.90	0.67-1.20	0.46
Insulin	1.21	0.58-2.50	0.61	0.63	0.36-1.12	0.12	0.82	0.58-1.15	0.26
Anticoagulant use (time-varying)	0.48	0.32-0.72	<.001	0.80	0.61-1.05	0.11	0.66	0.51-0.85	0.001
Statins	0.85	0.56-1.30	0.46	0.63	0.46-0.85	0.003	0.68	0.51-0.89	0.01
Angiotensin antagonists	0.70	0.46-1.07	0.10	0.95	0.68-1.33	0.77	0.91	0.67-1.24	0.56

* Relative to HbA1c 6% to <7%

HR= hazard ratio. CI= confidence interval.

Table S4. **Regression models analyzing the relationship between patient characteristics and the rate of stroke, after stratification by HbA1c before AF diagnosis.**

	HbA1c <6%			**HbA1c 6% to <7%**			**HbA1c 7% to <8%**			**HbA1c ≥8%**		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Diabetes duration (5 to <10 years)*	2.46	1.25-4.81	0.009	0.99	0.73-1.35	0.94	1.42	0.82-2.45	0.21	0.89	0.49-1.63	0.71
Diabetes duration (≥10 years)*	2.94	1.49-5.83	0.002	1.22	0.89-1.67	0.21	1.90	1.12-3.20	0.02	0.95	0.54-1.68	0.86
Age (per year)	1.04	1.01-1.07	0.007	1.04	1.02-1.05	<.001	1.01	0.98-1.03	0.64	1.06	1.03-1.09	<.001
Female sex	1.30	0.85-1.97	0.23	1.28	1.00-1.63	0.05	1.11	0.79-1.56	0.55	1.18	0.78-1.76	0.43
Heart Failure	0.96	0.61-1.51	0.85	1.12	0.86-1.46	0.39	1.22	0.86-1.75	0.27	0.81	0.52-1.25	0.34
Hypertension	0.81	0.36-1.84	0.62	1.51	0.85-2.67	0.16	3.02	1.10-8.30	0.03	0.77	0.41-1.45	0.42
Stroke or transient ischemic attack	2.90	1.45-5.81	0.003	2.18	1.37-3.49	0.001	4.28	2.56-7.16	<.001	2.40	1.24-4.64	0.009
Vascular disease	1.06	0.68-1.66	0.80	1.04	0.81-1.35	0.76	1.00	0.70-1.43	0.99	1.09	0.72-1.66	0.68
eGFR (per 10ml/min/1.73m2)	0.96	0.87-1.06	0.39	0.97	0.91-1.03	0.27	0.95	0.87-1.03	0.21	1.17	1.05-1.30	0.004
Oral hypoglycemics	1.08	0.70-1.67	0.72	1.17	0.91-1.52	0.22	1.25	0.77-2.02	0.37	0.76	0.45-1.26	0.28
Insulin	1.16	0.42-3.24	0.78	0.80	0.47-1.37	0.42	0.50	0.29-0.86	0.01	1.16	0.75-1.79	0.50
Time-varying anticoagulant use	0.68	0.43-1.06	0.09	0.63	0.49-0.81	<.001	0.68	0.48-0.97	0.03	0.78	0.52-1.17	0.23
Statins	0.88	0.56-1.40	0.60	0.80	0.61-1.07	0.13	0.42	0.29-0.60	<.001	0.72	0.46-1.15	0.17
Angiotensin antagonists	0.83	0.52-1.33	0.44	0.83	0.62-1.11	0.20	0.87	0.56-1.35	0.55	1.04	0.64-1.72	0.87

* Relative to diabetes duration <5 years

HR= hazard ratio. CI= confidence interval.

Table S5. Summary of the results of sensitivity analyses where the regression model was limited to the following subgroups: 1) patients who were not anticoagulated on the index date; 2) patients aged <75 years.

	No baseline anticoagulation			Age <75 years		
Variable	HR	95% CI	p-value	HR	95% CI	p-value
Diabetes duration (5 to <10 years) *	1.20	0.95-1.50	0.12	1.07	0.70-1.61	0.76
Diabetes duration (≥10 years) *	1.45	1.16-1.82	0.001	1.57	1.05-2.34	0.03
HbA1c <6%†	0.97	0.76-1.24	0.81	0.91	0.56-1.49	0.72
HbA1c 7% to <8%†	1.08	0.88-1.33	0.47	1.47	1.02-2.12	0.04
HbA1c category ≥8†	1.44	1.12-1.84	0.004	1.53	1.00-2.33	0.05
Age (per year)	1.03	1.02-1.04	<.001	1.04	0.98-1.10	0.18
Female sex	1.23	1.04-1.44	0.01	0.99	0.72-1.34	0.92
Hypertension	1.30	0.92-1.84	0.14	1.04	0.62-1.73	0.89
Heart failure	1.08	0.90-1.28	0.40	1.26	0.92-1.74	0.16
Stroke or transient ischemic attack	2.73	2.07-3.61	<.001	2.78	1.63-4.73	< .001
Vascular disease	1.04	0.88-1.24	0.65	0.96	0.71-1.32	0.82
eGFR (per 10ml/min/1.73m2)	0.99	0.95-1.03	0.60	0.95	0.89-1.02	0.18
Oral hypoglycemics	1.12	0.93-1.35	0.23	0.97	0.68-1.38	0.86
Insulin	0.82	0.63-1.08	0.16	0.82	0.55-1.23	0.34
Anticoagulant use (time-varying)	0.67	0.57-0.80	<.001	0.57	0.41-0.78	0.001
Statins	0.68	0.57-0.82	<.001	0.70	0.49-1.00	0.05
Angiotensin antagonists	0.87	0.72-1.07	0.18	1.02	0.69-1.51	0.92

* Relative to diabetes duration <5 years
† Relative to HbA1c 6% to <7%

Table S6. Summary of the results of sensitivity analyses where the outcome was limited to ischemic strokes.

	Hazard Ratio	95% confidence interval	p-value
Diabetes duration (relative to 1 to <5 years)	-	-	-
5 years to <10 years	1.18	0.93-1.51	0.17
≥10 years	1.39	1.10-1.77	0.01
HbA1c category (relative to 6% to <7%)	-	-	
<6%	0.94	0.72-1.22	0.64
7% to <8%	1.16	0.93-1.44	0.20
≥8%	1.50	1.16-1.95	0.002
Age (per year)	1.03	1.02-1.05	<.001
Female sex	1.35	1.13-1.61	0.001
Heart failure	1.07	0.89-1.29	0.48
Hypertension	1.32	0.91-1.92	0.15
Stroke or transient ischemic attack	2.82	2.11-3.78	<.001
Vascular disease	1.07	0.89-1.29	0.46
Estimated glomerular filtration rate per 10ml/min/1.73m2	1.00	0.95-1.04	0.86
Oral hypoglycemics	1.06	0.87-1.29	0.55
Insulin	0.81	0.61-1.08	0.16
Anticoagulant use (time-varying)	0.62	0.52-0.74	<.001
Statins	0.69	0.57-0.84	<.001
Angiotensin antagonists	0.88	0.72-1.09	0.25

Figure S1. Cohort flow diagram.