Association between glycemic control assessed by continuous glucose monitoring and stroke in patients with atrial fibrillation and diabetes mellitus

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Background: Both atrial fibrillation (AF) and diabetes mellitus (DM) are documented risk factors for stroke; however, whether glycemic control is associated with the prevalence of stroke remains unclear in patients with AF and DM. The purpose of this study was to investigate the association between glycemic control assessed by continuous glucose monitoring (CGM) and the risk of stroke.

Methods: In total, 510 AF patients with DM from April 2013 to June 2017 were included. The subcutaneous sensor of CGM was inserted after hospital admission and lasted for 72 consecutive hours. Time in range (TIR), a novel metric derived from CGM, was defined as the time spent in the target range (3.9–10 mmol/L). A logistic regression model was constructed by regarding TIR as a categorical variable and a continuous variable, respectively.

Results: The mean age of the 510 enrolled patients was 69.8 years. Patients who had previously suffered from stroke had a markedly lower TIR than those without diagnosed stroke (55.1%±19.0% *vs.* 64.2%±15.1%, P<0.001). Compared to patients with TIR ≤46%, the risk of stroke decreased significantly with increasing TIR quartiles: adjusted odds ratios (ORs) of 0.80 for TIR of 46–65%, 0.64 for TIR of 65–81%, and 0.59 for TIR of >81% (all P<0.001). Taking TIR as a continuous variable, the adjusted OR was 0.89 [95% confidence interval (CI): 0.82–0.95] per 10% increment in TIR.

Conclusions: This study found that better TIR is independently associated with a decreased risk of stroke in patients with AF and DM.

Keywords: Glycemic control; continuous glucose monitoring; stroke; atrial fibrillation (AF); diabetes mellitus (DM)

Introduction

Atrial fibrillation (AF) is characterized by irregular electrical activity and myocardial contraction of the atrium, and is an important cause of disability and death in elderly people (1,2). In a worldwide epidemiological study, the estimated global prevalence of individuals with AF was 33.5 million adults (20.9 million men and 12.6 million women) in 2010 (3). According to data from the United States, the number of AF patients in 2010 was estimated to be 5.2 million, which is expected to rise to 12.1 million by

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2030 (4). Antithrombotic therapy has been demonstrated to dramatically reduce the risk of stroke; however, these agents are associated with absolute increases in the events of major extracranial hemorrhage (5). Thus, the risk of bleeding limits the wide usage of anticoagulants, which has contributed to the stable occurrence of stroke in AF patients from 2000 to 2010 (6). For this reason, effective and safe interventions are needed to relieve the burden of stroke in clinical practice.

Diabetes mellitus (DM) is an independent risk factors for the incidence of stroke in patients of all ages (7), and also significantly increases the risk of stroke recurrence (8). DM is included in the congestive heart failure, hypertension, age >75 years, diabetes mellitus, prior stroke and TIA (CHADS$_2$) and the congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, stroke (doubled)—vascular disease, age 65–74 and sex category (female) CHA$_2$DS$_2$-VASc scores in AF patients, which has been recommended for stroke prediction by clinical guidelines [2019] (9). AF patients with DM are associated with an increased risk of hospitalization and death compared to those without DM (10). However, evidence of the association between glycemic control assessed by hemoglobin A1c (HbA1c) and the risk of stroke in AF patients with DM is inconsistent (11,12). With the technological advances in recent years, continuous glucose monitoring (CGM) has been shown to provide information of glucose levels in the body's interstitial fluid over a number of days continuously, and reflects more details of intra- and inter-day glycemic excursions compared to HbA1c (13). Time in range (TIR), a novel metric generated from CGM, is usually defined as the time that a patient spends within the range from 3.9 to 10.0 mmol/L (14). TIR is used to evaluate glycemic control and has been demonstrate to be associated with the progression of diabetic retinopathy (15) and cardiovascular mortality (16) in patients with DM. To date, little is known about the relationship between TIR and stroke among AF patients with DM.

This study aims to investigate the association of TIR derived from CGM with the risk of stroke in AF patients with DM. This study conducted a logistic regression analysis, reviewing a large number of high references, this paper is very novel in TIR with AF and DM research. This article is very valuable in research conclusions and discussions.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-2198).

Methods

Study populations

From April 2013 to June 2017, AF patients with DM aged ≥18 years were recruited from the local hospital. The diagnoses of AF and DM were determined by systematic medical history review and careful clinical examination. DM was diagnosed according to the 2020 American Diabetes Association criteria (17). Paroxysmal AF referred to an AF duration of ≤7 days, and persistent AF was defined as AF lasting >7 days. Patients with cardiac rhythm devices, diabetic ketoacidosis, mental disorders, cancer, and severe kidney or liver dysfunction were excluded from the study. Finally, a total of 510 AF patients with DM were enrolled in the analysis. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of The Second Hospital of Shanxi Medical University (NO.: 2013-023) and informed consent was taken from all the patients.

Data collection

Data on age, gender, smoking status, history of hypertension, chronic heart failure and vascular disease, and anticoagulation drug use of each participant was collected through a standardized data collection form. Next, each subject underwent a physical examination of height and weight. After a 10-hour overnight fast, a venous blood sample was drawn to test HbA1c using high-performance liquid chromatography. Each patient's CHA2DS2-VASc score was calculated based on the recommendations of 2019 American Heart Association/American College of Cardiology/American Heart Rhythm Society (AHA/ACC/HRS) guidelines (9). We also examined the patients' previous medical records to confirm the occurrence of stroke.

CGM and TIR

A continuous glucose detection system (Medtronic Inc., CA) was used for subcutaneous interstitial glucose monitoring. The sensor was inserted after hospital admission and lasted for 72 consecutive hours, providing a total of 864 glucose values. TIR was defined as the time spent in a patient's target range (3.9–10 mmol/L) over a 24-hour period. Other parameters, including the standard deviation (SD) of glucose values and the glucose coefficient of variation (CV), were also calculated. All patients adhered to their previous

Table 1 Characteristics of study participants by stroke history

	Stroke	No stroke	P
N	48	462	
Age, years	70.3±12.1	68.1±9.4	0.012
Age >75 years, n (%)	13 (27.1)	103 (22.3)	0.007
Male, n (%)	21(43.8)	235(50.9)	0.022
Body mass index (BMI), kg/m^2	26.7±3.5	25.8±2.7	0.128
Hypertension, n (%)	32 (66.7)	277 (60.0)	0.003
Chronic heart failure, n (%)	5 (10.4)	40 (8.7)	0.570
Anticoagulant use, n (%)	34 (70.8)	301 (65.5)	0.102
CHA$_2$DS$_2$-VASc score	5.61±1.43	3.72±0.97	<0.001
AF type, n (%)			0.012
Paroxysmal	19 (39.6)	232 (50.2)	
Persistent	29 (60.4)	230 (49.8)	
Hemoglobin A1c (HbA1c), %	8.2±1.7	7.4±2.1	<0.001

diet and therapy regimen.

Statistical analysis

Categorical variables were expressed as a number (percentage), and were compared between different groups by the Chi-square test. Continuous variables with normal distributions were expressed as means ± SD, and compared by the Student's t tests between the stroke and no stroke groups or one-way analysis of variance among patients with different TIR quartiles. A binary logistic regression model was used to estimate the independent association between TIR and the prevalence of stroke, after controlling for potential confounders including age, sex, Body Mass Index (BMI), hypertension, chronic heart failure, anticoagulation drug use, AF type, CHA2DS2-VASc score, and HbA1c. The binary logistic regression model was constructed by regarding TIR as a categorical variable (four categories according to the TIR quartiles: ≤46%, 46–65%, 65–81%, and >81%) and as a continuous variable, respectively. Differences were considered significant with a two-tailed P value <0.05. IBM SPSS Statistics 21.0 (IBM, Armonk, NY, USA) was used for statistical analysis.

Results

In total, 510 AF patients with T2DM were included

in our study. The enrolled patients had a mean age of 69.8±8.3 years, and 49.1% of them were male. Forty-eight participants had a documented history of stroke. Compared to the no stroke group, the stroke group were older and predominantly women (*Table 1*). Furthermore, patients with a history of stroke had a higher CHA2DS2-VASc score and HbA1c levels compared to those without a known stroke history. However, the two patient groups had similar proportions of anticoagulant use and chronic heart failure.

Based on the TIR quartiles, all of the patients were stratified into four groups: quartile 1 (Q1, ≤46%), quartile 2 (Q2, 46–65%), quartile 3 (Q3, 65–81%), and quartile 4 (Q4, >81%). The characteristics of the study participants by TIR quartiles are shown in *Table 2*. Among the 510 AF patients with T2DM, 137 (26.8%) had a TIR value ≤46%, 119 (23.3%) had a TIR value between 46% and 65%, 141 (27.6%) had a TIR value between 65% and 81%, and 113 (22.2%) had a TIR value >81%. Patients with a TIR >81% were younger, and were more likely to have a lower BMI, be using anticoagulants, and have a lower CHA2DS2-VASc score. These patients were also less likely to have been diagnosed with persistent AF.

Figure 1A demonstrates that, compared with those without a stroke diagnosis, subjects who had previously suffered from stroke had a significantly lower percentage of TIR (55.1%±19.0% *vs.* 64.2%±15.1%, P<0.001). Patients with a TIR >81% experienced low rates of stroke (10.1%). In comparison, 12.8% of patients with TIR ≤46% had a prior stroke. As shown in *Figure 1B*, the prevalence of stroke increased with the descending TIR quartiles (P for trend <0.001); the prevalence of stroke was 10.1% in Q4, 10.7% in Q3, 11.9% in Q2, and 12.8% in Q1.

Our multinomial logistic regression analysis with TIR as a categorical variable (quartiles) showed that the TIR in Q4 was independently associated with a low risk of stroke when subjects with TIR in Q1 were taken as the reference group (*Table 3*). In model 1, we adjusted for age, sex, and BMI. Model 2 was adjusted for all factors in model 1 plus hypertension, chronic heart failure, anticoagulant use, and AF type. Model 3 further adjusted for the CHA2DS2-VASc score and HbA1c based on model 2. Compared to patients with TIR ≤46%, the risk of stroke decreased significantly with increasing TIR quartiles: adjusted ORs of 0.80 (95% CI: 0.68–0.92) for the TIR in Q2, 0.64 (95% CI: 0.53–0.79) for Q3, and 0.59 (95% CI: 0.50–0.74) for the highest quartile (P for trend <0.001).

When TIR was included as a continuous variable, the association between TIR and the prevalence of stroke

Table 2 Characteristics of study participants by time in range (TIR) quartiles

	Q1 (≤46%)	Q2 (46–65%)	Q3 (65–81%)	Q4 (>81%)	P
N	137	119	141	113	
Age, years	72.2±7.1	70.3±8.7	69.0±7.4	67.7±9.2	0.008
Age >75 years, n (%)	30 (21.9)	25 (21.0)	28 (19.9)	23 (20.4)	0.253
Male, n (%)	65 (47.4)	60 (50.7)	69 (48.9)	55 (48.6)	0.009
BMI, kg/m^2	27.0±2.6	26.7±2.4	25.8±2.1	25.6±2.3	0.003
Hypertension, n (%)	84 (61.3)	74 (62.2)	89(63.1)	69 (61.1)	0.005
Chronic heart failure, n (%)	15 (10.9)	11 (9.2)	14 (10.0)	11 (9.7)	0.496
Anticoagulant drug use, n (%)	9 (65.6)	8 (67.2)	10 (70.9)	8 (70.8)	0.012
CHA$_2$DS$_2$-VASc score	6.21±1.32	5.62±1.16	4.98±1.26	5.10±1.37	<0.001
Atrial Fibrillation (AF) type					0.001
Paroxysmal	38.6	40.3	48.8	49.7	
Persistent	61.4	59.7	51.2	50.3	
HbA1c, %	9.2±1.2	8.6±1.8	7.7±1.6	7.1±1.3	<0.001
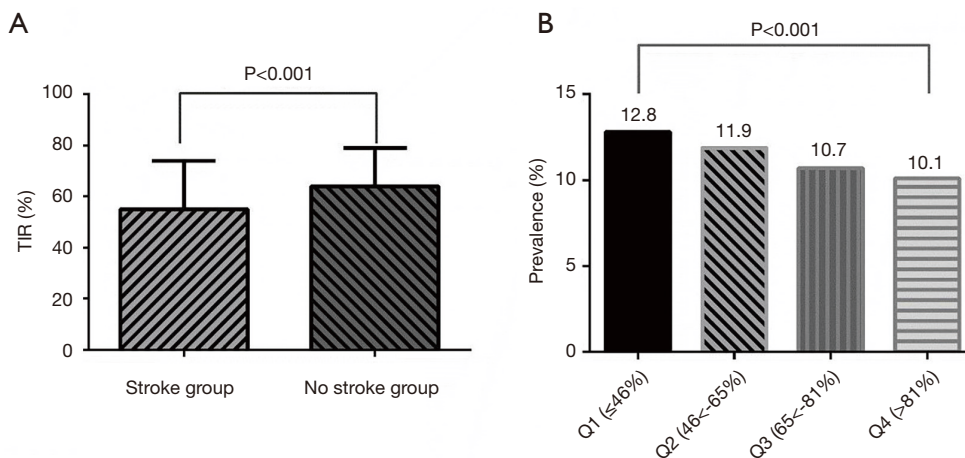
Figure 1 Time in range (TIR) levels in different groups and the prevalence of stroke among patients with different TIR quartiles. (A) TIR levels according to the history of stroke; (B) prevalence of stroke in different TIR quartiles.

appeared to be significant, with an adjusted OR of 0.93 (95% CI: 0.85–0.98, P=0.008) after adjusting for age, sex, and BMI in model 1 (*Table 4*). After further adjustment for hypertension, chronic heart failure, anticoagulant use, and AF type in model 2, the effect of TIR on the presence of stroke remained significant (*Table 4*). The adjusted OR in model 3 was 0.89 (95% CI: 0.82–0.95) per 10% increment in TIR.

Discussion

In this cross-sectional study of 510 AF patients with DM, we observed that patients who had a stroke previously had significantly lower levels of TIR assessed by CGM. After adjusting for potential confounding factors, including CHA2DS2-VASc score and HbA1c, we found that higher levels of TIR were strongly associated with a decrease in

Table 3 Associations between time in range (TIR) quartiles and stroke after adjusting for potential confounders

	TIR				
	Q1 (≤46%)	Q2 (46–65%)	Q3 (65–81%)	Q4 (>81%)	P value
Univariate analysis	1.00 (Reference)	0.87 (0.73, 0.95)	0.73 (0.64, 0.83)	0.70 (0.61, 0.81)	<0.001
Model 1	1.00 (Reference)	0.86 (0.72, 0.95)	0.71 (0.61, 0.81)	0.66 (0.58, 0.80)	<0.001
Model 2	1.00 (Reference)	0.84 (0.70, 0.93)	0.68 (0.59, 0.80)	0.62 (0.54, 0.78)	<0.001
Model 3	1.00 (Reference)	0.80 (0.68, 0.92)	0.64 (0.53, 0.79)	0.59 (0.50, 0.74)	<0.001

Model 1 was adjusted for age, sex, and BMI. Model 2 was adjusted for all factors in model 1 plus hypertension, chronic heart failure, anticoagulant use, and atrial fibrillation (AF) type. Model 3 was adjusted for all factors in model 2 plus CHA_2DS_2-VASc score and HbA1c.

Table 4 Associations between per 10% time in range (TIR) increase and stroke after adjusting for potential confounders

	Stroke	P value
Model 1	0.93 (0.85, 0.98)	0.008
Model 2	0.91 (0.84, 0.96)	0.004
Model 3	0.89 (0.82, 0.95)	0.001

Model 1 was adjusted for age, sex, and BMI. Model 2 was adjusted for all factors in model 1 plus hypertension, chronic heart failure, anticoagulant use, and AF type. Model 3 was adjusted for all factors in model 2 plus CHA_2DS_2-VASc score and HbA.

the risk of stroke. In addition, this independent association seemed to exhibit a dose-response linear pattern. These results support the validity of TIR as a surrogate marker of glycemic control for long-term clinical outcomes beyond stroke. With the increase in living standards, high blood pressure, hyperglycemia and high blood fat patients are increasing, and metabolic syndrome is significantly increased in the population, and these are related to the development of trembling. The incidence of atrial fibrillation increased year by year, and the risk of stroke and death, which made the social burden, but the treatment method was slow. At this point, controlled factors such as blood pressure, blood sugar and blood lipids are especially important, and exercise and lifestyle changes promote atrial fibrillation management and treatment.

The risk of diabetes complications in type 2 diabetic patients is significantly related to sustained hyperglycemia. At present, HbA1c is recognized as the gold standard for evaluation of glycemic control, and a decrease in the HbA1c level significantly slows the progression of microvascular complications in diabetic patients (18). The association between TIR and stroke confirmed in our study is consistent with the findings of a previous study, which showed that glycemic control assessed by HbA1c was directly associated with the risk of stroke in AF subjects with diabetes (12). However, there are several limitations of HbA1c, such as anemia, recent blood transfusion, end-stage kidney disease, pregnancy, and ethnic difference, which may lead to discrepancies between the HbA1c result and the subject's true mean glycemia (19). Moreover, HbA1c reflects average glycemia in the previous 3 months, but it cannot detect the details of hypoglycemia, hyperglycemia, and glycemic variability. Instead, TIR, which reflects the time spent in the target glucose range, can provide information beyond HbA1c and guide optimal diabetes management. Increasing evidence has reported that TIR levels are associated with the risk of microvascular complications in patients with DM (15,20). To the best of our knowledge, this study is the first to link TIR assessed by CGM to the risk of stroke in AF patients with DM during hospitalization.

Blood glucose variability compared to persistent hyperglycemia in diabetic hyperglycemia, blood glucose variability is more harmful to diabetic patients. Further, the blood glucose variability in diabetic patients significantly improves the level of cognitive dysfunction of patients with acute cerebral stroke and inhibits the treatment of cognitive dysfunction. Blood glucose variability and diabetic patients and patients with diabetic patients are closely related, and blood sugar fluctuations should be controlled clinically, which is conducive to improving the prognosis of patients. Therefore, while lowering blood sugar levels, effectively control blood sugar fluctuations.

The association between diabetes mellitus and stroke in AF patients has been demonstrated in the atrial fibrillation cohort study (21) and the Swedish AF cohort study (22). Several mechanisms may accompany diabetes-induced stroke, including endothelial cell dysfunction, vascular

smooth muscle dysfunction, impaired platelet functions, and abnormal coagulation (23). Diabetes is believed to trigger endothelial cell dysfunction by excessive release of free fatty acids and breaking the balance between nitric oxide bioavailability and accumulation of reactive oxidative species (24). Hyperglycemia, a key manifestation of diabetes, contributes to the development and progress of these abnormalities, as demonstrated by the association between hyperglycemia and poor thrombotic outcomes (25). Hence, these aforementioned mechanisms may partially account for the findings of our study. Similarly, a thrombogenic tendency could be seen in patients with AF due to abnormal changes in blood flow, anatomical and structural changes in vessel walls, and abnormal platelet activation (26). Thus, the second potential explanation of our result is that hyperglycemia activates thrombogenesis in the left atrium of AF patients, which leads to an increased risk of stroke. Hyperglycemia causes neurological defects in stroke, the mortality rate is increased, and the prognosis is deteriorated. The optimum blood sugar concentration is 3–5 mmol/L. Appropriately limit the intake of glucose in stroke, give a certain amount of insulin treatment to prevent high blood sugar It may help improve prognosis. Diet should be controlled and regularly quantified. Add the blood glucose drug after controlling, which is the high blood sugar after meal, and the amount of blood sugar is adjusted according to the blood glucose. We can use a dynamic blood glucose monitoring for blood glucose.

In recent decades, the CHA2DS2-VASc score has been the most commonly used scheme, which enables the precise identification of the high risk of a stroke event (score ≥2) among AF patients (27). Our findings support the necessity of maintaining or even strengthening the status of hypoglycemic therapy in patients with a high risk of stroke. However, the precision of this scheme to stratify patients with a CHA2DS2-VASc score of 1 is poor. According to guideline recommendations, "either warfarin or aspirin" can be used for patients with a CHA2DS2-VASc score of 1 (28), and thus, the best treatment for these patients is unclear. The clinical implication of our study is that CGM-assessed TIR might be a biomarker for refining the stroke risk and guiding the choice of antithrombotic medication in these individuals. In the past decade, considerable progress has been made in reducing the cost and improving the accuracy of CGM. Now, we can apply our findings to the real world by providing CGM assessments of inpatients and making the appropriate changes in therapy based on this information.

The main strength in our study is the large sample size of AF patients with DM who were assessed by CGM for 3 days, and this is the first study to investigate the association between TIR measured by CGM and the risk of stroke. However, this study also has several limitations that should be noted. Firstly, we could not distinguish between type 1 diabetes (T1DM) and type 2 diabetes (T2DM). However, taking the mean age of participants and the prevalence of T2DM in the general population into account, we expect the majority of participants to be T2DM. Secondly, the TIR levels with 3-day CGM may not reflect the participants' historical glycemic control; however, we attempted to minimize the influence of this by enrolling patients with stable medication over the previous 3 months. Thirdly, the observational design of our study means that we could not demonstrate the causal relationship between TIR levels and the risk of stroke. Prospective studies and clinical trials are needed to evaluate the role of TIR in predicting stroke outcome in patients with AF and DM.

In conclusion, we found that TIR, as a novel metric of glycemic control, was independently associated with the risk of stroke in AF patients with DM. Our findings imply that an achievable better TIR should be encouraged to decrease the risk of stroke.

Acknowledgments

Footnote

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of The Second Hospital of Shanxi Medical University (NO.: 2013-023) and informed consent was taken from all the patients.

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