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Abnormal glucose regulation increases stroke risk in minor ischemic stroke or TIA

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ABSTRACT

Objective: To investigate whether abnormal glucose regulation contributes to a new stroke in patients with a minor ischemic stroke or TIA.

Methods: We derived data from the Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events trial. Patients with a minor stroke or TIA were categorized into 3 groups: patients with diabetes mellitus (DM), impaired fasting glucose (IFG), and normal fasting plasma glucose. The primary outcome was a new stroke (ischemic or hemorrhagic) at 90 days. We assessed the association between glucose regulation status and risk of stroke by multivariable Cox regression models adjusted for potential covariates.

Results: Among 5,135 included patients, 1,587 (30.9%), 409 (8.0%), and 3,139 (61.1%) patients were identified as DM, IFG, and normal glucose, respectively. Compared with normal glucose, IFG (11.0% vs 6.9%; adjusted hazard ratio [adj HR] 1.57, 95% confidence interval [CI] 1.13–2.19) and DM (15.8% vs 6.9%; adj HR 2.38, 95% CI 1.97–2.88) were associated with increased risk of stroke at 3 months after a minor stroke or TIA after adjusted for potential covariates. We found a weak J-shaped association between fasting plasma glucose and risk of stroke with a nadir of 4.9 mmol/L.

Conclusions: Both IFG and DM were associated with an increased risk of stroke in patients with a minor stroke or TIA.

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GLOSSARY

CHANCE = Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events; **CI** = confidence interval; **DM** = diabetes mellitus; **HR** = hazard ratio; **IFG** = impaired fasting glucose; **IGT** = impaired glucose tolerance.

Diabetes mellitus (DM) is an established independent risk factor of stroke recurrence in patients with ischemic stroke or TIA.[1–3] Some[4,5] but not all[6] previous studies also showed that the risk of recurrent stroke is already raised in prediabetic stages, with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). However, the previous study focused on patients with minor ischemic stroke or TIA only reported the association of IGT, but not IFG, with risk of stroke.[4] Additionally, previous studies found a J-shaped relationship between baseline nonfasting glucose levels and stroke risk in patients with minor stroke or TIA,[4] and also between admission serum glucose and functional outcome at 12 months in patients with general ischemic stroke with a nadir of 5 mmol/L.[7] However, a similar curve for fasting plasma glucose in patients with a minor stroke or TIA was never reported. Therefore, the pattern and magnitude of association between abnormal glucose regulation, especially IFG, and risk of stroke in patients with a minor stroke or TIA should be further examined. The aim of this study is to investigate the association of abnormal glucose regulation and risk of stroke after a minor stroke or TIA.

Supplemental data at Neurology.org

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METHODS **Study participants.** We derived data from the Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial. Details on the rationale, design, and major results of the CHANCE trial have been published previously.[8–10] Briefly, CHANCE is a randomized, double-blind, controlled trial conducted at 114 hospitals in China between October 2009 and July 2012, in which 5,170 patients within 24 hours after onset of a minor stroke or high-risk TIA were randomized to the group of clopidogrel plus aspirin or aspirin alone. Patients in the trial met the following criteria: age 40 years or older, diagnosis of an acute minor ischemic stroke (NIH Stroke Scale ≤3) or high-risk TIA (ABCD^2 ≥4), and able to initiate the study drug within 24 hours after onset.

Standard protocol approvals, registrations, and patient consents. The CHANCE trial is registered at clinicaltrials.gov (registration number: NCT00979589). The protocol and data collection of the CHANCE trial was approved by the ethics committee of Beijing Tiantan Hospital and all other study centers. All participants or their representatives provided written informed consent before being entered into the study.

Baseline data collection. Baseline data on demographics, history of DM, and other cardiovascular risk factors, such as ischemic stroke, TIA, myocardial infarction, coronary heart disease, atrial fibrillation, hypertension, hypercholesterolemia, and smoking status, were collected through face-to-face interviews by trained interviewers (neurologists from participating hospitals). Plasma glucose after overnight fasting was performed within the first 2 days after admission. DM was defined as a self-reported history of physician-diagnosed diabetes or use of hypoglycemic medications (e.g., insulin, sulfonylureas, or biguanides) during hospitalization or fasting plasma glucose on admission ≥7.0 mmol/L.[2] The diagnosis of IFG was based on the American Diabetes Association criteria of fasting blood glucose ≥6.1 mmol/L and <7.0 mmol/L.[11] Normal fasting plasma glucose was indicated by fasting glucose <6.1 mmol/L.

Table 1 Baseline characteristics of the patients by glucose regulation status

Characteristics	DM (n = 1,587)	IFG (n = 409)	Normal (n = 3,139)	p Value
Age, y, median (IQR)	62.9 (55.8–72.1)	61.5 (53.6–71.2)	62.0 (54.2–71.0)	0.004
Female, n (%)	632 (39.8)	138 (33.7)	971 (30.9)	<0.001
Medical history, n (%)				
Ischemic stroke	342 (21.6)	80 (19.6)	604 (19.2)	0.17
TIA	62 (3.9)	11 (2.7)	100 (3.2)	0.31
Myocardial infarction	47 (3.0)	10 (2.4)	37 (1.2)	<0.001
Angina	70 (4.4)	18 (4.4)	95 (3.0)	0.03
Congestive heart failure	29 (1.8)	8 (2.0)	43 (1.4)	0.39
Known atrial fibrillation or flutter	26 (1.6)	5 (1.2)	65 (2.1)	0.35
Valvular heart disease	3 (0.2)	1 (0.2)	10 (0.3)	0.72
Hypertension	1,147 (72.3)	268 (65.5)	1,961 (62.5)	<0.001
Hypercholesterolemia	243 (15.3)	34 (8.3)	292 (9.3)	<0.001
Smoking status, n (%)				<0.001
Never smoking	1,001 (63.1)	242 (59.2)	1,687 (53.7)	
Previous smoker	164 (10.3)	31 (7.6)	319 (10.2)	
Current smoker	422 (26.6)	136 (33.2)	1,133 (36.1)	
Index event, n (%)				0.68
Minor stroke	1,145 (72.1)	302 (73.8)	2,253 (71.8)	
TIA	442 (27.9)	107 (26.2)	886 (28.2)	
NIHSS score on admission, median (IQR)	2 (0–2)	2 (1–3)	1 (0–2)	<0.001
Mean ± SD time to randomization, h	12.6 ± 6.9	12.8 ± 7.1	12.7 ± 7.0	0.80
Time to randomization, h, n (%)				0.87
<12	782 (49.3)	201 (49.1)	1,570 (50.0)	
≥12	805 (50.7)	208 (50.9)	1,569 (50.0)	
Antiplatelet therapy, n (%)				0.03
Aspirin only	799 (50.3)	229 (56.0)	1,540 (49.1)	
Clopidogrel + aspirin	788 (49.7)	180 (44.0)	1,599 (50.9)	
Antihypertensive therapy, n (%)	583 (36.9)	146 (36.0)	1,072 (34.4)	0.25

Abbreviations: DM = diabetes mellitus; IFG = impaired fasting glucose; IQR = interquartile range; NIHSS = NIH Stroke Scale.

Outcome assessment. The primary outcome was a new stroke (ischemic or hemorrhagic) during the 90-day follow-up period.[9] Secondary outcomes included a new composite vascular event (ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death), death from any cause, and TIA. All reported events were verified by a central adjudication committee that was blinded to the study group assignments.

Statistical analysis. We presented continuous variables as mean ± SD or median with interquartile range and categorical variables as percentages. Baseline variables among different statuses of glucose regulation were compared by one-way analysis of variance or Kruskal-Wallis test for continuous and χ^2 test for categorical variables.

To examine the interaction effect of glucose regulation status by treatment group assignment, we tested the statistical significance of glucose regulation status × treatment group assignment in a multivariable Cox model. We further assessed the associations between glucose regulation status and prognosis of minor stroke or TIA using multivariable Cox regression models. Adjusted hazard ratios (HRs) and their 95% confidence intervals (CI) were calculated. We performed 2 models. In the first model, we adjusted only age and sex. In the second model, we included all the potential confounders listed in table 1.

We further evaluated the pattern and magnitude of associations between fasting plasma glucose and risk of stroke using a Cox regression model with restricted cubic splines for fasting plasma glucose adjusting for covariates. Fasting plasma glucose of 4.9 mmol/L was treated as the reference and the 5 knots for spline were placed at the 5th, 25th, 50th, 75th, and 95th percentiles of fasting plasma glucose. In sensitivity analysis, we excluded patients with history of diabetes or hypoglycemic medications during hospitalization to exclude the potential influence of hypoglycemic medications on the effects of plasma glucose.

Two-sided p values < 0.05 were considered to be statistically significant. All analyses were conducted with SAS software version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Study participants and characteristics. A total of 5,170 patients with a minor ischemic stroke or TIA were enrolled in the CHANCE trial. After excluding 35 patients with missing data of fasting plasma glucose on admission, 5,135 patients were included in the analysis. Among the 5,135 patients, the average age was 62.6 years (range 34–96), and 1,741 (33.9%) were female.

Table 2 Risk of stroke at 3 months after a minor stroke or TIA by glucose regulation status

Outcomes	Glucose regulation status	No.	Events, n (%)	Model 1[a]		Model 2[b]	
				Adjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Stroke	Normal	3,139	216 (6.9)	1		1	
	IFG	409	45 (11.0)	1.68 (1.22-2.33)	0.002	1.57 (1.13-2.19)	0.007
	DM	1,587	251 (15.8)	2.49 (2.07-3.00)	<0.001	2.38 (1.97-2.88)	<0.001
Composite events[c]	Normal	3,139	218 (6.9)	1		1	
	IFG	409	45 (11.0)	1.66 (1.20-2.30)	0.002	1.56 (1.12-2.16)	0.008
	DM	1,587	257 (16.2)	2.52 (2.10-3.04)	<0.001	2.42 (2.00-2.92)	<0.001
Ischemic stroke	Normal	3,139	204 (6.5)	1		1	
	IFG	409	43 (10.5)	1.69 (1.21-2.36)	0.002	1.59 (1.14-2.23)	0.007
	DM	1,587	249 (15.7)	2.62 (2.17-3.16)	<0.001	2.52 (2.07-3.05)	<0.001
Hemorrhagic stroke	Normal	3,139	12 (0.4)	1		1	
	IFG	409	2 (0.5)	1.75 (0.38-8.20)	0.47	1.15 (0.23-5.71)	0.87
	DM	1,587	2 (0.1)	0.37 (0.08-1.70)	0.20	0.23 (0.04-1.26)	0.09
Myocardial infarction	Normal	3,139	1 (0.03)	1		1	
	IFG	409	0 (0.0)	—		—	
	DM	1,587	4 (0.3)	7.25 (0.78-67.81)	0.08	14.95 (1.15-194.16)	0.04
Death from any cause	Normal	3,139	9 (0.3)	1		1	
	IFG	409	4 (1.0)	3.35 (0.98-11.41)	0.054	3.20 (0.83-12.39)	0.09
	DM	1,587	7 (0.4)	1.59 (0.58-4.33)	0.37	1.33 (0.44-4.04)	0.62
Transient ischemic attack	Normal	3,139	52 (1.7)	1		1	
	IFG	409	3 (0.7)	0.56 (0.17-1.79)	0.33	0.64 (0.20-2.08)	0.46
	DM	1,587	30 (1.9)	1.20 (0.76-1.91)	0.44	1.23 (0.77-1.99)	0.39

Abbreviations: CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; IFG = impaired fasting glucose.
[a] Model 1: Adjusted for age and sex.
[b] Model 2: Adjusted for age, sex, history of ischemic stroke, TIA, myocardial infarction, angina, congestive heart failure, known atrial fibrillation or flutter, valvular heart disease, hypertension, hypercholesterolemia, smoking status, index event, NIH Stroke Scale on admission, time to randomization, and antiplatelet and antihypertensive therapy.
[c] Composite events: Stroke, myocardial infarction, or death from cardiovascular causes.

Table 3 Risk of stroke at 3 months for clopidogrel-aspirin combined therapy compared with aspirin alone by glucose regulation status

	Aspirin		Clopidogrel-aspirin		Model 1[a]			Model 2[b]		
Glucose regulation status	No.	Events, n (%)	No.	Events, n (%)	Adjusted HR (95% CI)	*p* Value	*p* Value for interaction	Adjusted HR (95% CI)	*p* Value	*p* Value for interaction
Normal	1,540	123 (8.0)	1,599	93 (5.8)	0.70 (0.53–0.92)	0.01	0.90	0.69 (0.52–0.91)	0.008	0.69
IFG	229	29 (12.7)	180	16 (9.0)	0.74 (0.37–1.47)	0.38		0.65 (0.29–1.44)	0.29	
DM	799	150 (18.8)	788	101 (12.8)	0.68 (0.52–0.87)	0.003		0.64 (0.50–0.84)	0.001	

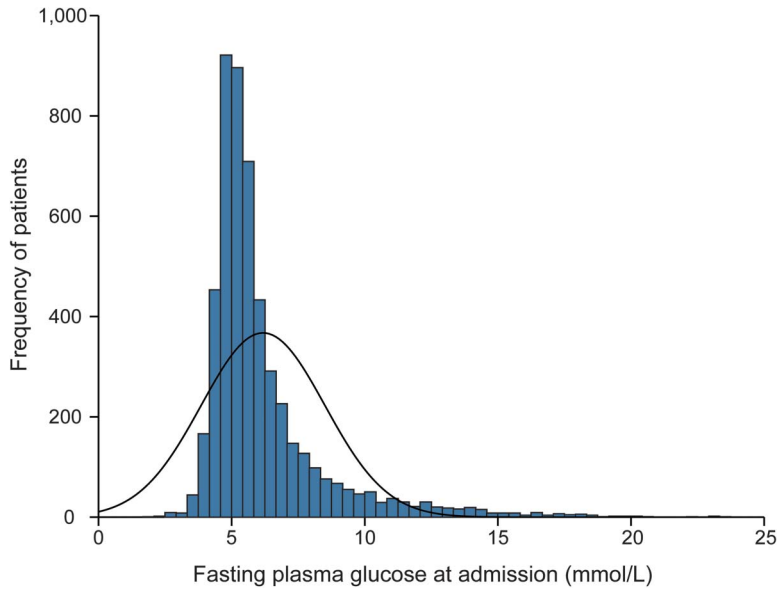
Abbreviations: CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; IFG = impaired fasting glucose.
[a] Model 1: Adjusted for age and sex.
[b] Model 2: Adjusted for age, sex, history of ischemic stroke, TIA, myocardial infarction, angina, congestive heart failure, known atrial fibrillation or flutter, valvular heart disease, hypertension, hypercholesterolemia, smoking status, index event and NIH Stroke Scale score on admission, time to randomization, and antihypertensive therapy.

Among the 5,135 patients, there were 1,587 (30.9%), 409 (8.0%), and 3,139 (61.1%) patients identified as DM, IFG, and normal fasting plasma glucose, respectively. Patients with DM were older, were more likely to be female, had more vascular risk factors (such as myocardial infarction, angina, hypertension, and hypercholesterolemia), were less likely to be current smokers, and had higher severity of index event on presentation (table 1).

Association of glucose regulation status with risk of stroke. Table 2 shows the 3-month risk of stroke after a minor stroke or TIA across categories of glucose regulation status. There were 512 (10.0%) new stroke occurrences at 3 months, among which 496 (96.9%) were ischemic stroke and 16 (3.1%) were hemorrhagic stroke. There was no interaction effect of antiplatelet therapy by categories of glucose regulation status for the risk of stroke (p for interaction = 0.69 in the fully adjusted model) (table 3). Compared with patients with normal glucose regulation, patients with IFG had approximately 1.5-fold increased risk of stroke at 3 months after full adjustment for potential covariates (11.0% vs 6.9%; adjusted HR = 1.57, 95% CI 1.13–2.19), whereas those with DM had approximately 2.5-fold increased risk of stroke at 3 months after full adjustment for potential covariates (15.8% vs 6.9%; adjusted HR = 2.38, 95% CI 1.97–2.88) (table 2). Similar results were found for the endpoints of composite vascular events and ischemic stroke. An association with few number of events was found between DM and risk of myocardial infarction (p = 0.04). No significant association was found between IFG, DM, and outcome of hemorrhagic stroke, death from any cause, and TIA.

The fasting plasma glucose on admission was skewed distributed with a median of 5.5 (interquartile range 4.9–6.5) mmol/L (figure 1). Using a Cox regression model with restricted cubic spline, we found a weak J-shaped association between fasting plasma glucose and risk of stroke with a nadir of 4.9 mmol/L (figure 2A). A similar curve was observed after excluding patients with history of diabetes or hypoglycemic medications during hospitalization in sensitivity analysis (figure 2B).

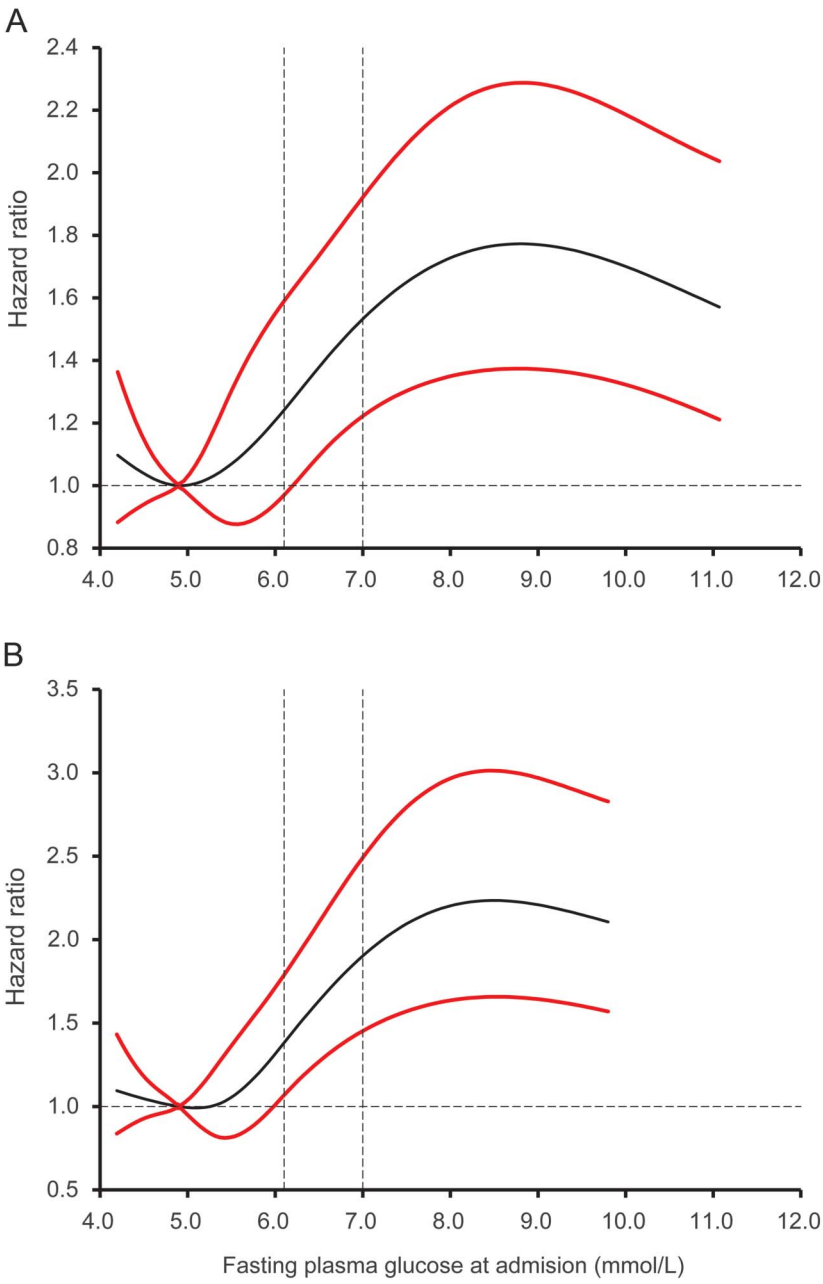
Figure 1 Distributions of fasting plasma glucose on admission



DISCUSSION In this post hoc analysis of the CHANCE trial, we found that both IFG and DM were associated with an increased risk of stroke recurrence in patients with a minor ischemic stroke or TIA. Furthermore, we also found a weak J-shaped association between fasting plasma glucose and risk of stroke with a nadir of 4.9 mmol/L.

DM was an established risk factor of new stroke in patients with general ischemic strokes,[1] lacunar strokes,[12] and TIAs.[13] The ABCD[2] score recommended for predicting early stroke risk following TIA includes DM as an important factor (1 point).[13,14] As expected, DM was a significant risk factor of new stroke in patients with a minor stroke or TIA

Figure 2 Adjusted hazard ratios of stroke according to fasting plasma glucose on admission



(A) All participants. (B) Participants without history of diabetes or hypoglycemic medications. The black line indicates adjusted hazard ratio and the red lines the 95% confidence interval bands. Reference is fasting glucose of 4.9 mmol/L. Data were fitted using a Cox regression model of restricted cubic spline with 5 knots (5th, 25th, 50th, 75th, 95th percentiles) for fasting plasma glucose, adjusting for potential covariates. The lowest 5% and highest 5% of participants are not shown in the figures owing to small sample sizes.

in our study. However, few studies investigated the association between prediabetes and risk of new stroke in patients with a minor stroke and TIA. Previous studies showed that the risk of stroke is already raised in prediabetic stages, including IFG and IGT, in patients with ischemic stroke or TIA.[4,5] Our previous study showed that prediabetes was an independent predictor for the mortality but not stroke recurrence of patients with general ischemic strokes.[6] Post hoc analysis in the Dutch TIA Trial showed that IGT was significantly associated with increased future stroke in nondiabetic patients with TIA or minor ischemic stroke.[4] Our study added the evidence that IFG, which had different pathophysiologic mechanisms from IGT,[5] was also associated with increased risk of new stroke in patients with a minor stroke and TIA. Compared with 2-hour postload plasma glucose, fasting plasma glucose is an easier to perform measure in clinical practice. Minor ischemic strokes and TIAs account for approximately 40%–60% of all strokes.[15,16] It is reported that the prevalence of prediabetes in nondiabetic patients with recent stroke or TIA ranges from 23% to 53%.[5,17] Therefore, it is of clinical significance to highlight early identification of abnormal glucose regulation to predict the prognosis of patients with minor strokes and TIAs.

Hypoglycemia is associated with focal and global brain damage and dysfunction resulting in an increased risk for cardiovascular poor outcomes.[4,18] Although the sample size for patients with hypoglycemia was small in this study, we still found a weak increased risk of stroke in patients with plasma glucose of <4.9 mmol/L. The weak J-shaped association between fasting plasma glucose and risk of stroke in patients with minor stroke or TIA in our study was similar to the J-shaped relationship between baseline nonfasting glucose levels and stroke risk in patients with minor stroke or TIA[4] and between admission serum glucose and functional outcome in patients with general ischemic stroke.[7] Although reversible neurologic symptoms could be attributed to hypoglycemia and we cannot exclude the possibility that nonischemic TIA mimics caused by hypoglycemia were enrolled, this cannot make a difference for the results of this study since the proportion of nonischemic TIA mimics could be very small.

This study has several limitations. First, the definition of DM in this analysis was based on self-reported history of physician diagnosis of DM on admission or hypoglycemic agents use during hospitalization and we did not collect new cases of DM after discharge, which may have caused misclassification of DM groups. Second, oral glucose tolerance test was not performed and data of 2-hour postload plasma glucose were not available. The association between IGT and risk of stroke cannot be estimated in this study. Third, the characteristics of TIA patients enrolled in this study were different from that of a typical TIA sample from population-based cohorts.[19] This study enrolled only high-risk TIA patients (ABCD^2 scores ≥4), which may have resulted in high events rates. Fourth, it was difficult to distinguish between stress hyperglycemia and diabetes, since plasma glucose was tested only once and HbA1c was not available in the CHANCE trial. Recent study suggested that the

association between admission hyperglycemia and poor outcome of acute ischemic stroke reflects stress response rather than a deleterious effect of glucose.[20] Fifth, the baseline data of etiology classification for enrolled patients were not collected in the trial and we could not investigate the association between abnormal glucose regulation and stroke prognosis by stroke mechanism. Furthermore, we acknowledged the possibility that residual confounding (i.e., highest prevalence of hypertension in DM, then in IFG and those with normal glucose) might have influenced the association between abnormal glucose regulation and risk of stroke. Finally, the sample sizes for patients with low (<4.0 mmol/L) and high (>12 mmol/L) fasting plasma glucose were small. The results found in this study need to be further validated in studies with larger sample size.

Our results demonstrated that abnormal glucose regulation, including both impaired fasting glucose and diabetes, was associated with an increased risk of stroke in patients with a minor ischemic stroke or TIA.

AUTHOR CONTRIBUTIONS

Yuesong Pan: study concept and design, analysis and interpretation of data, drafting the manuscript. Jing Jing: acquisition of data. Hao Li: analysis and interpretation of data. Yongjun Wang: obtaining funding, study supervision or coordination. Yilong Wang: study concept and design, acquisition of data, analysis and interpretation of data. Yan He: study concept and design, analysis and interpretation of data, drafting the manuscript.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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