

The Relationship Between Fasting Blood Glucose Levels and First Ischemic Stroke in Elderly Hypertensive Patients

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Objective: The relationship between fasting blood glucose and first ischemic stroke in older adults was unclear, so we explored this association among older patients with hypertension in China.

Methods: We recruited hypertensive participants with 60 or more of age. Fasting blood glucose concentrations were categorized into quartiles. Hazard ratio (HR) and 95% confidence interval (CI) for ischemic stroke were estimated using multivariate Cox regression analysis and subgroup analysis.

Results: A total of 3310 (1474 (44.53%) male) patients with mean age of 71.41±7.20 years were included. During the mean follow-up period of 5.5 years, 206 cases of ischemic stroke occurred. After adjusting for potential confounding variables, multivariate adjusted HRs for each standard deviation increment of fasting blood glucose, the risk of ischemic stroke increased by 11% (95% CI: 1.03, 1.21; P= 0.008). In addition, when using the lowest group (Q1) as reference, the multivariate adjusted HRs for first ischemic stroke were 1.76 (95% CI: 1.08, 2.86; P=0.023), 1.73 (95% CI: 1.06, 2.81; P=0.027) and 2.42 (95% CI: 1.49, 3.93; P<0.001) (P for trend<0.001). Subgroup analysis revealed that the association between fasting blood glucose and the risk of ischemic stroke was higher in male (HR: 1.22 vs 1.10), those with uncontrolled hypertension (HR: 1.22 vs 1.10), subjects with diabetes (HR: 1.19 vs 1.10), overweight (HR: 1.19 vs 1.09), smoking habits (HR: 1.33 vs 1.13) and those whose eGFR< 90 (HR: 1.16 vs 1.09).

Conclusion: Fasting blood glucose was an independent risk factor for the first ischemic stroke among older adults with hypertension. Managing fasting blood glucose may be beneficial for participants with diabetes, poorly controlled blood pressure, had smoking habits, being overweight, and with reduced renal function.

Keywords: fasting blood glucose, ischemic stroke, elderly, hypertension, community

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Introduction

Stroke is the main cause of death in China,¹ with ischemic stroke to be the most common subtype.² Ischemic stroke is a type of arteriosclerotic disease and a heterogeneous disease.³ Studies have shown that elevated blood pressure, age, obesity, smoking, hyperlipidemia, impaired fasting glucose, elevated fasting blood glucose (FBG), diabetes and hyperglycemia were independent risk factors for ischemic stroke.³ Although previous studies have reported significant associations between FBG and arteriosclerotic cardiovascular disease,⁴⁻⁷ the relationship between FBG and ischemic stroke was still controversial. Some studies reported that the relationship between

stroke and FBG was linear, U-shaped or J-shaped among general population,⁸ asymptomatic adults,⁹ patients with pre-existing atherothrombotic diseases,¹⁰ or non-diabetic population.^{6,11} In addition, there was a study demonstrated that FBG had no null association with the risk of cardiovascular diseases, such as coronary heart disease and ischemic stroke in hypertensive patients.¹² Given the inconsistent relationship between fasting blood glucose and first ischemic stroke in older adults with hypertension, we explored the association among older hypertensive patients with hypertension in China.

Materials and Methods

Study Subjects

This retrospective cohort study enrolled 3500 older patients from January, 2010, to December, 2011, at Guangdong community in China. We recruited essential hypertensive patients who were at least 60 years of age. We excluded participants with missing data on blood pressure (n=37), FBG (n=5) or physical examination (n=16), and those who had a stroke history at baseline (n=132). Eventually, 3310 participants were included for data analysis (Figure 1). Informed consent was obtained from all included participants. This study was in compliance with the principles outlined in the Declaration of Helsinki and was approved by the institutional medical ethical committee the Guangdong Provincial People's Hospital, Guangzhou, China.

Measurement of Indicators

Demographic information was obtained from all patients through questionnaires, including age, sex, habits on

smoking and drinking, a previous history of diseases (such as diabetes, coronary heart disease, and stroke), and combined medication history (such as antihypertensive drugs, hypoglycemic drugs, and lipid-lowering drugs). Parameters being measured in the physical examination and laboratory tests included height, weight, and blood pressure, urinalysis, FBG, blood lipid and creatinine after overnight fasting. Drinking status was defined as having consumed at least 50g alcohol daily in the last 30 days and smoking was defined as using at least 100 cigarettes during their lifetime in the last 30 days before the survey of the present study.¹³ Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg or/and diastolic blood pressure (DBP) ≥ 90 mmHg, or currently taking antihypertensive medication or self-reported.¹⁴ Diabetes was defined as FBG ≥ 11.1 mmol/L, or currently taking hypoglycemic agents or self-reported.¹⁵ Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Estimate glomerular filtration rate (eGFR) was calculated by using the simplified equation on the modification of diet.

All stroke cases were ascertained from the local medical insurance system of the medical insurance bureau, and patients without medical records were followed up by telephone or by face-to-face in the community until 31 December 2016. Hospitalization with a diagnosis of ischemic stroke was confirmed by computed tomography or magnetic resonance image and checked by discharge data.

Statistical Analysis

All the continuous variables were presented as mean \pm standard deviation, and categorical variables were presented in

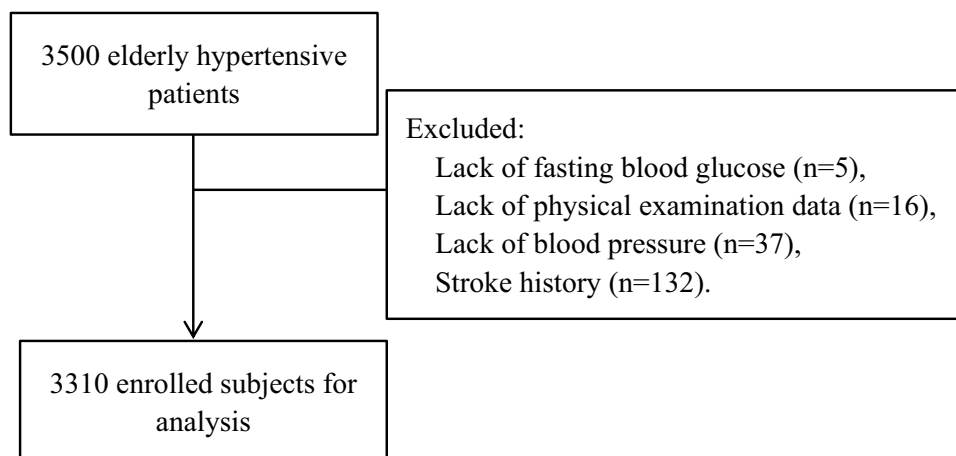


Figure 1 Research flow chart.

frequency or as a percentage according to baseline FBG categories. FBG concentrations were grouped by quartiles (Q1: < 4.39mmol/l, Q2: 4.40–5.79 mmol/l, Q3: 5.80–6.36 mmol/l, and Q4: \geq 6.37 mmol/l). Subgroup differences by FBG quartiles were identified by the One-Way ANOVA, Kruskal–Wallis *H*-test and chi-square tests. Hazard ratios (HRs) and 95% confidence intervals (CIs) for ischemic stroke were estimated using multivariate Cox regression analysis. The Model I only included FBG. The model II was adjusted for age, sex and BMI. The model III was adjusted for sex, BMI, age, diabetes history, coronary heart disease history, antihypertensive drugs, statins, SBP, DBP, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), smoking, drinking and eGFR. Subgroup analysis was conducted according to sex (male or female), age (<70, 70–80 or \geq 80 years), SBP (<140 or \geq 140 mm Hg), eGFR (<90 or \geq 90 mL/min/1.73m²), BMI (<25 or \geq 25 kg/m²), the history of diabetes (yes or no), drinking status (yes or no), smoking status (yes or no), using statins (yes or no) and taking antihypertensive drug (yes or no), and the interactions between FBG and subgroups on the association with stroke were tested. A 2-sided *P*<0.05 was considered statistically significant. All statistical analyses were performed using R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of the Participants

After applying the inclusion and exclusion criteria, 3310 older hypertensive patients were included, 1474 (44.53%) were males. The mean age was 71.41 ± 7.20 years old. Baseline characteristics of the participants are presented in Table 1. There were significant differences in age, BMI, SBP, DBP, triglyceride, LDL-C, HDL-C, sex, smoking status, diabetes history and taking antihypertensive drugs and statins across the quartile groups.

The Relationship Between Fasting Blood Glucose Levels and Ischemic Stroke

As showed in Table 2, during an average follow-up of 5.5 years, 206 cases of ischemic strokes occurred. When FBG was treated as continuous variable, FBG was significantly associated with ischemic stroke in model I (HR=1.15, 95% CI: 1.08, 1.23; *P*<0.001). In model II, FBG was still an independent risk factor for ischemic stroke (HR=1.14, 95% CI: 1.07, 1.23; *P*<0.001), as well as the fully adjusted

model (model III), where FBG (HR=1.11, 95% CI: 1.03, 1.21; *P*=0.008) was positively associated with the first occurrence of ischemic stroke (Table 2). When using the lowest quartile of FBG as reference, the HRs for ischemic stroke from Q2 to Q4 were 1.77 (95% CI: 1.10, 2.87, 1.90 (95% CI: 1.18, 3.07) and 3.08 (95% CI: 1.97, 4.83) (*P* trend<0.001) in model I. In model III, the HRs for the first occurrence of ischemic stroke increased in parallel with the quartiles of FBG (HRs were 1.76 (95% CI: 1.08, 2.86), 1.73 (95% CI: 1.06, 2.81), and 2.42 (95% CI: 1.49, 3.93) from the second to the fourth quartiles, respectively, *P* trend<0.001) (Table 2). Multivariate adjusted smoothing spline plots suggested that FBG levels have a nonlinear relationship with the first occurrence of ischemic stroke (Figure 2).

The Results of Subgroup Analyses

As shown in Table 3, subgroup analysis revealed that the association between FBG and risk of ischemic stroke was appear to be stronger in male (HR: 1.22 vs 1.10), those with uncontrolled hypertension (HR: 1.22 vs 1.10), subjects with diabetes (HR: 1.19 vs 1.10), overweight (HR: 1.19 vs 1.09), smoking habits (HR: 1.33 vs 1.13), drinking habits (HR: 1.17 vs 1.05), without using statins (HR: 1.19 vs 1.09), without taking antihypertensive drugs (HR: 1.16 vs 1.10) and those with eGFR< 90 (HR: 1.16 vs 1.09).

Discussion

In the present study, elevated FBG levels were significantly associated with increased risk for the first incident of ischemic stroke and this relationship appeared as a gradually increasing nonlinear relationship. The risk might further elevate for subjects combined with diabetes, poorly controlled blood pressure, smoking, being overweight, and with reduced renal function.

We found that the risk for first ischemic stroke gradually increased with FBG concentration. The result of the present study agreed with previous cohort analyses among adults with hypertension.^{12,16} Our study did not find a clear threshold for the relationship between FBG and ischemic stroke among older adults with hypertension. Our results might suggest a J-curve nor a U-curve relationship, which was also suggested in some other studies.^{4,8,10,17,18} In addition, a meta-analysis of 102 prospective studies demonstrated that among people without diabetes, FBG concentration had modest and non-linear relation with stroke risk.¹⁹ The reason why our research results differ from previous may be

Table 1 Baseline Characteristics of Participant Patients by Quartiles of Fasting Blood Glucose

	All	Q1	Q2	Q3	Q4	P-value
Number	3310	810(<4.39mmol/l)	836(4.40–5.79 mmol/l)	829(5.80–6.36 mmol/l)	835(≥6.37 mmol/l)	
Age(years)	71.41 ± 7.20	72.25 ± 7.06	71.61 ± 7.01	71.40 ± 7.09	70.39 ± 7.50	<0.001
BMI(kg/m ²)	23.91 ± 3.80	23.30 ± 3.72	23.36 ± 3.44	23.94 ± 3.63	24.03 ± 4.14	<0.001
SBP(mmHg)	131.08 ± 17.23	128.47 ± 15.76	129.94 ± 16.99	132.02 ± 17.36	133.83 ± 18.23	<0.001
DBP(mmHg)	78.33 ± 9.55	77.47 ± 9.19	78.05 ± 9.53	78.58 ± 9.54	79.21 ± 9.85	0.002
TC(mg/dl)	203.07 ± 45.66	203.28 ± 47.84	204.31 ± 42.27	202.19 ± 43.43	202.50 ± 48.88	0.791
Triglyceride (mg/dl)	150.11 ± 116.12	136.15 ± 114.06	136.80 ± 95.11	147.48 ± 107.17	180.39 ± 138.77	<0.001
LDL-C(mg/dl)	103.63 ± 29.43	102.52 ± 27.95	105.04 ± 29.19	105.09 ± 29.89	101.85 ± 30.55	0.047
HDL-C(mg/dl)	50.76 ± 14.03	51.31 ± 16.71	51.51 ± 12.78	50.83 ± 13.03	49.38 ± 13.15	0.010
eGFR(mL/min/1.73m ²)	90.42 ± 34.21	91.95 ± 39.49	88.29 ± 36.65	86.60 ± 30.70	94.82 ± 37.49	0.426
Sex(n, %)						0.002
Male	1474 (44.53%)	388 (47.90%)	396 (47.37%)	360 (43.43%)	330 (39.52%)	
Female	1836 (55.47%)	422 (52.10%)	440 (52.63%)	469 (56.57%)	505 (60.48%)	
Smoking(n, %)						0.002
No	2377 (71.81%)	552 (68.15%)	582 (69.62%)	610 (73.58%)	633 (75.81%)	
Yes	933 (28.19%)	258 (31.85%)	254 (30.38%)	219 (26.42%)	202 (24.19%)	
Drinking(n, %)						0.719
No	2972 (89.79%)	730 (90.12%)	742 (88.76%)	746 (89.99%)	754 (90.30%)	
Yes	338 (10.21%)	80 (9.88%)	94 (11.24%)	83 (10.01%)	81 (9.70%)	
Diabetes(n, %)						<0.001
No	2805 (84.74%)	771 (95.19%)	781 (93.42%)	747 (90.11%)	506 (60.60%)	
Yes	505 (15.26%)	39 (4.81%)	55 (6.58%)	82 (9.89%)	329 (39.40%)	
CAD(n, %)						0.352
No	3276 (98.97%)	804 (99.26%)	828 (99.04%)	822 (99.16%)	822 (98.44%)	
Yes	34 (1.03%)	6 (0.74%)	8 (0.96%)	7 (0.84%)	13 (1.56%)	
Antihypertensive drugs(n, %)						<0.001
No	2158 (65.20%)	584 (72.10%)	579 (69.26%)	531 (64.05%)	464 (55.57%)	
Yes	1152 (34.80%)	226 (27.90%)	257 (30.74%)	298 (35.95%)	371 (44.43%)	
Beta-blocker(n, %)						<0.001
No	3155 (95.32%)	778 (96.05%)	808 (96.65%)	797 (96.14%)	772 (92.46%)	
Yes	155 (4.68%)	32 (3.95%)	28 (3.35%)	32 (3.86%)	63 (7.54%)	
CCB(n, %)						<0.001
No	2656 (80.24%)	693 (85.56%)	692 (82.78%)	654 (78.89%)	617 (73.89%)	
Yes	654 (19.76%)	117 (14.44%)	144 (17.22%)	175 (21.11%)	218 (26.11%)	
ACEI(n, %)						0.006
No	3099 (93.63%)	775 (95.68%)	789 (94.38%)	769 (92.76%)	766 (91.74%)	
Yes	211 (6.37%)	35 (4.32%)	47 (5.62%)	60 (7.24%)	69 (8.26%)	
ARB(n, %)						<0.001
No	2667 (80.57%)	676 (83.46%)	699 (83.61%)	657 (79.25%)	635 (76.05%)	
Yes	643 (19.43%)	134 (16.54%)	137 (16.39%)	172 (20.75%)	200 (23.95%)	
Statins(n, %)						<0.001
No	3025 (91.39%)	752 (92.84%)	771 (92.22%)	771 (93.00%)	731 (87.54%)	
Yes	285 (8.61%)	58 (7.16%)	65 (7.78%)	58 (7.00%)	104 (12.46%)	

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary heart disease; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2 Relationship Between Fasting Blood Glucose Levels and the First Occurrence of Ischemic Stroke in Different Models

	Case/Total	Model I	Model II	Model III
		HR(95% CI) P-value	HR(95% CI) P-value	HR(95% CI) P-value
FBG(per SD increased)	206/3310	1.15 (1.08, 1.23) <0.001	1.14 (1.07, 1.23) <0.001	1.11 (1.03, 1.21) 0.008
FBG (quartile)				
Q1	27/810	ref	ref	ref
Q2	48/836	1.77 (1.10, 2.87) 0.019	1.79 (1.10, 2.90) 0.018	1.76 (1.08, 2.86) 0.023
Q3	51/829	1.90 (1.18, 3.07) 0.008	1.87 (1.16, 3.02) 0.010	1.73 (1.06, 2.81) 0.027
Q4	80/835	3.08 (1.97, 4.83) <0.001	2.89 (1.83, 4.55) <0.001	2.42 (1.49, 3.93) <0.001
P for trend		<0.001	<0.001	<0.001

Notes: Model I adjust for: none. Model II adjust for: sex, BMI, age. Model III adjust for: sex, BMI, age, diabetes history, coronary heart disease history, antihypertensive drugs, statins, SBP, DBP, TC, TG, LDL-C, HDL-C, smoking, drinking and eGFR.

Abbreviations: FBG, fasting blood glucose; Q, quartile; SD, standard deviation, HR, hazard ratios; CI, confidence interval.

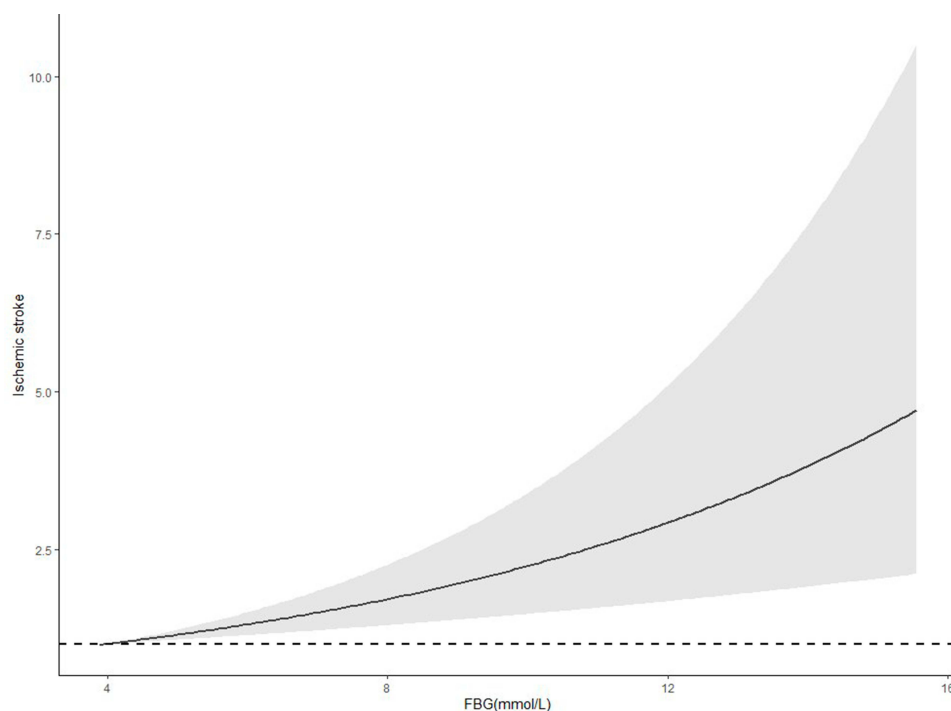
due to the selected population and ethnicities of these studies are different.

In our study, older hypertensive patients combined with diabetes, poorly controlled blood pressure, smoking, being overweight, with reduced renal function might have a higher risk for ischemic stroke. Smoking, elevated SBP, obesity and diabetes were established risk factors for ischemic stroke,³ which was likely the explanation for our findings. Our results were also consistent with previous studies^{20–23} and current international

recommendations for stroke prevention and treatment.^{3,24}

Individuals should stop smoking, limit or avoid alcohol, maintaining good control on weight, blood pressure, blood sugar and blood lipids for stroke prevention.^{25–28}

However, some limitations should be taken into consideration in the present study. First, FBG was measured only once at baseline, so we were not able to examine the effects of FBG changes with stroke. Second, we did not adjust for several confounding factors were adjusted, such as the history of atrial fibrillation, the levels of uric acid

**Figure 2** The relationship between fasting blood glucose levels and the first occurrence of ischemic stroke.

Abbreviations: FBG, fasting blood glucose; HR, hazard ratios; CI, confidence interval.

Table 3 Effect Size of Fasting Blood Glucose Levels on the First Occurrence of Ischemic Stroke in Subgroups

	Number	HR(95% CI)	P-value	P Interaction
Sex				0.318
Male	1474	1.22 (1.09, 1.36)	<0.001	
Female	1836	1.10 (1.04, 1.23)	0.003	
Age				0.298
<70	1640	1.23 (1.09, 1.38)	<0.001	
≥70, <80	1204	1.11 (1.01, 1.22)	0.037	
≥80	466	1.07 (1.05, 1.46)	0.043	
Diabetes				0.084
No	2805	1.10 (1.05, 1.34)	0.034	
Yes	505	1.19 (1.07, 1.18)	0.002	
Smoking				0.091
No	2377	1.13 (1.05, 1.22)	0.001	
Yes	933	1.33 (1.12, 1.57)	<0.001	
Drinking				0.939
No	2972	1.05 (1.08, 1.23)	0.031	
Yes	338	1.17 (1.03, 1.53)	0.027	
Taking antihypertensive drugs				0.843
No	2158	1.16 (1.08, 1.24)	<0.001	
Yes	1152	1.10 (1.04, 1.50)	0.033	
Statins				0.571
No	3025	1.19 (1.07, 1.23)	0.002	
Yes	285	1.09 (1.04, 1.46)	0.040	
SBP				0.458
<140	2356	1.10 (1.04, 1.35)	0.003	
≥140	954	1.22 (1.06, 1.43)	<0.001	
BMI				0.300
<25	2122	1.09 (1.02, 1.21)	0.005	
≥25	1188	1.19(1.08, 1.32)	0.031	
eGFR				0.927
<90	1518	1.16 (1.04, 1.34)	0.008	
≥90	1792	1.09 (1.03, 1.27)	0.016	

Notes: When analysis a subgroup variable, sex, BMI, age, diabetes history, coronary heart disease history, antihypertensive drugs, statins, SBP, DBP, TC, TG, LDL-C, HDL-C, smoking, drinking and eGFR were all adjusted expect itself.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; HR, hazard ratios; CI, confidence interval.

and homocysteine. Third, the history of diabetes in this study was mainly obtained from self-reported history and we did not have the data of glycated hemoglobin. Finally, the present study did not distinguish the relationship between FBG and different subtypes of stroke.

Conclusion

In conclusion, among elderly hypertensive patients, FBG was closely related to the first occurrence of ischemic stroke. The relationship was stronger for subjects

combined with diabetes, poorly controlled blood pressure, smoking, being overweight, and with reduced renal function.

Abbreviations

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; Q, quartile; HR, hazard ratios; CI, confidence interval.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflict of interest.

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