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ORIGINAL ARTICLES

Predictive value of fibrinogen for early neurological deterioration in large-artery atherosclerotic cerebral infarction

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Abstract

Background & Objective: To evaluate the predictive value of fibrinogen at admission for early neurological deterioration (END) in patients with large artery atherosclerotic (LAA) stroke without reperfusion therapy. Fibrinogen, a glycoprotein crucial for clotting, is associated with worse outcomes in ischemic stroke patients. While its connection with thrombolytic therapy's prognosis is recognized, its predictive role for non-thrombolytic-treated patients is less clear. The objective of this study is to evaluate the predictive value of fibrinogen at admission for early neurological deterioration (END) in patients with large artery atherosclerotic (LAA) stroke without reperfusion therapy. *Methods:* This retrospective case-control study included consecutive inpatients with LAA stroke admitted within 72 h of onset at the Fifth Affiliated Hospital of Sun Yat-Sen University between January 2021 and December 2021. An increase of ≥2 in the National Institutes of Health Stroke Scale (NIHSS) within 7 days after admission was defined as END. *Results:* This study included 179 patients (121 males); the mean age was 62.67±13.51 years. There were 42 and 137 patients in the END and non-END groups. The NIHSS score at admission was higher in the END group than in the non-END group, the fibrinogen levels were higher, and the uric acid levels were lower (all P<0.05). NIHSS at admission (OR=1.086, 95%CI: 1.001-1.179), fibrinogen levels (OR=2.182, 95%CI: 1.286-3.702), and uric acid levels (OR=0.995, 95%CI=0.990-0.999) were independently associated with END. Receiver-operating characteristic curve analysis suggested that the sensitivity, specificity, and area under the curve for fibrinogen for END were 62.9%, 78.1%, and 0.730 (95% CI: 0.532-0.828, P<0.009), respectively.
Conclusions: Elevated fibrinogen is independently associated with END in patients with LAA stroke without reperfusion therapy.

Keywords: Risk factors, acute ischemic stroke, atherosclerosis, neurologic deficits, fibrinogen

INTRODUCTION

Stroke refers to a neurological deficit due to an acute focal injury of the central nervous system by ischemic infarction or blood collection within the brain or ventricular system.[1] Ischemic strokes (80%-87% of all strokes) result from large artery atherosclerosis (LAA) (embolus or thrombosis), cardioembolism (often from atrial fibrillation), small vessel occlusion (lacunar), or systemic hypoperfusion.[1,2] Acute ischemic stroke is a major cause of death and disability worldwide.[2,3] In low- and middle-income countries, stroke incidence, prevalence, and mortality are 281, 393, and 105 per 100,000 person-years, respectively.[4] LAA stroke is the major type of ischemic stroke.[5] In addition to intravenous thrombolysis and endovascular treatment at the very early stage, there is no other specific treatment for LAA stroke, which is prone to deterioration and poor prognosis.[6] Furthermore, reperfusion therapy has a strict time window limitation, and less than 10% of the patients receive reperfusion therapy.[7]

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Early neurological deterioration (END) is a complication of stroke and is defined as an increase in the National Institutes of Health Stroke Scale (NIHSS) score ≥2 at 72 h from baseline NIHSS[8,9], although various definitions have been reported.[8,10,11] Although the incidence of END is relatively low, it increases morbidity and mortality.[12] In patients who underwent thrombolysis, large vessel disease (LVD) with carotid stenosis, other LVD, intracerebral hemorrhage, and ischemic stroke were correlated to END.[12] Still, there are no effective predictors and prevention measures for END in patients with LAA without reperfusion therapy. Previously, progressive ischemic stroke in LAA after intravenous thrombolysis or endovascular treatment was reported to be associated with elevated plasma fibrinogen, high blood pressure, high serum glucose, occlusion site, and thrombus length.[13-15]

Fibrinogen is a large fibrous glycoprotein composed of three pairs of polypeptides linked by a large number of disulfide bonds. Its terminal and middle globular domains are connected by α-helical coiled-coil rods. On the platelet surface, fibrinogen can bind to the activated αIIbβ3 integrin, leading to platelet aggregation due to the intercellular bridges responsible. The process is crucial for hemostasis but is also involved in various adhesion and inflammatory functions in other cell types.[16] Hyperfibrinogenemia predicts the long-term risk of death in patients with ischemic stroke.[17] The sustained increase of plasma fibrinogen during ischemic stroke predicts worse outcomes independently of baseline fibrinogen level.[18] In patients with a history of ischemic stroke or TIA, the fibrinogen levels are linearly correlated to the risk of recurrence.[19] At admission for acute ischemic stroke, high plasma fibrinogen is associated with poor outcomes.[15] Therefore, high admission fibrinogen levels can be a marker of short-term prognosis in acute patients with ischemic stroke treated with thrombolytic therapy.[15] Still, whether fibrinogen levels can also be used to predict poor short-term outcomes in patients not receiving thrombolytic therapy is not clearly known. Therefore, this study aimed to evaluate the predictive value of fibrinogen levels at admission for END in patients with LAA stroke without reperfusion therapy.

METHODS

Study design and patients

This retrospective study included consecutive patients treated at the comprehensive stroke center of The Fifth Affiliated Hospital of Sun Yat-Sen University (Zhuhai City, China) from January 2021 to December 2021. The study was approved by the ethics committee of The Fifth Affiliated Hospital of Sun Yat-Sen University. The requirement for individual consent was waived by the committee because of the retrospective nature of the study.

All included patients had LAA stroke and did not receive reperfusion therapy. The inclusion criteria were 1) >18 years of age, 2) admission within 72 h of onset, 3) acute stroke diagnosed by computer tomography (CT) or/and magnetic resonance imaging (MRI), 4) LAA according to the TOAST classification based on CT angiography (CTA) or MRI angiography (MRA)[20], 5) without reperfusion therapy, 6) modified Rankin Score (mRS) ≤2 before the stroke, and 7) with complete data. The exclusion criteria were 1) a history of depression, cognitive dysfunction, or other psychiatric disorders (which can bias the NIHSS assessment), 2) unconscious, severe aphasia, or dysarthria (preventing the adequate determination of the NIHSS), or 3) traumatic brain injury.

Data collection and definition

All patients were managed according to a standardized protocol and care pathway based on current guidelines.[21] The baseline demographic data, vascular risk factors, stroke-related information, and laboratory data were collected from the medical records and included age, sex, smoking status, hypertension, diabetes mellitus, hyperlipidemia, history of prior TIA, prior ischemic stroke, ischemic heart disease, use of antithrombotic, antihypertensive, antidiabetic, or statin medications, systolic blood pressure (SBP), diastolic blood pressure (DBP), white blood cells (WBC), fibrinogen, creatinine, uric acid, fasting blood glucose (FBG), glycated hemoglobin (HbA1c), triglycerides (TG), total cholesterol (T-CH), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), homocysteine, and the NIHSS score on admission. Neuroimages were examined by a radiologist and a neurologist, and the results were obtained by consensus. Cerebral circulation affected by the stroke was determined based on

imaging and classified as anterior circulation/posterior circulation or both.

The patients who experienced END during hospitalization were grouped as the END group; otherwise, they were grouped as the non-END group. END was defined as an NIHSS score increase of ≥2 within 7 days after admission.[22]

Statistical analysis

The continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. The continuous data with a normal distribution were presented as means ± standard deviations (SD) and analyzed using Student's t-test; otherwise, they were presented as medians (interquartile ranges (IQRs)) and analyzed using the Mann-Whitney U-test. The categorical variables were presented as n (%) and analyzed using the chi-square test or Fisher's exact test. Multivariable logistic regression analysis was used to explore the factors associated with END. The variables with P<0.05 in the univariable analyses were entered into the multivariable analysis. The results were presented as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Receiver operating characteristic (ROC) curves were used to evaluate the accuracy of plasma fibrinogen levels to predict END in patients with LAA stroke without reperfusion therapy. The area under the curve (AUC) was calculated as a measurement of the accuracy of the test. All statistical analyses were performed with SPSS 25.0 for Windows (IBM, Armonk, NY, USA). Two-sided P-values <0.05 were considered statistically significant.

RESULTS

Characteristics of the patients

This study included 179 patients (121 males); mean age of 62.67±13.51 years. There were 42 patients in the END group and 137 in the non-END group. Table 1 shows the baseline clinical characteristics of the patients. The END group had significantly higher proportions of patients with

Table 1: Comparison of baseline clinical characteristics between the END and Non-END groups

Clinical characteristic	Total (n=179)	END (n=42)	Non-END (n=137)	P
Age (years), mean ± SD	62.67 ± 13.51	63.69 ± 12.82	62.36 ± 13.74	0.577
Male, n (%)	121 (67.6%)	27 (64.3%)	94 (68.6%)	0.600
Smoker, n (%)	79 (44.1%)	21 (50.0%)	58 (42.3%)	0.382
Hypertension, n (%)	113 (63.1%)	33 (78.6%)	80 (58.4%)	0.018*
Diabetes mellitus, n (%)	37 (20.7%)	6 (14.3%)	31 (22.6%)	0.243
Hyperlipidemia, n (%)	9 (5.0%)	1 (2.4%)	8 (5.8%)	0.370
Prior TIA or ischemic stroke, n (%)	31 (17.3%)	8 (19.1%)	23 (16.8%)	0.735
Ischemic heart disease, n (%)	10 (5.6%)	3 (7.1%)	7 (5.1%)	0.616
Antithrombotic medication use, n (%)	15 (8.4%)	5 (11.9%)	10 (7.3%)	0.346
Antihypertensive medication use, n (%)	63 (35.2%)	20 (47.6%)	43 (31.4%)	0.054
Antidiabetic medication use, n (%)	30 (16.8%)	5 (11.9%)	25 (18.3%)	0.336
Statin use, n (%)	7 (3.9%)	4 (9.5%)	3 (2.2%)	0.032*
Initial SBP, mmHg, median (IQR)	155 (139-168)	152 (139-174)	155 (140-167)	0.954
Initial DBP, mmHg, median (IQR)	90 (82-98)	90 (83-97)	90 (80-98)	0.702
NIHSS at admission, median (IQR)	4 (2-7)	5 (2-8)	3 (1-6)	0.019*
Cerebral circulation affected by stroke, n (%)				
Anterior circulation	113 (63.13%)	28 (66.67%)	85 (62.04%)	0.189
Posterior circulation	46 (25.70%)	7 (16.67%)	39 (28.47%)	
Both	20 (11.17%)	7 (16.67%)	13 (9.49%)	

* P<0.05.

END: early neurological deterioration; SD: standard deviation; TIA: transient ischemic attack; SBP: systolic blood pressure; DBP: diastolic blood pressure; IQR: interquartile range; NIHSS: National Institutes of Health Stroke Scale.

hypertension (78.6% vs. 58.4%, P=0.018) and statin use (9.5% vs. 2.2%, P<0.032) compared with the non-END group, but there were no significant differences between groups in age, sex, smoking status, diabetes mellitus, hyperlipidemia, history of prior TIA/stroke, family history of stroke or coronary heart disease, or use of antithrombotic, antihypertensive, or antidiabetic medication. The NIHSS score at admission was significantly higher in the END group than in the non-END group (5 [2-8] vs. 3 [1-6], P<0.019). There were no significant differences between the two groups regarding stroke location, SBP, and DBP.

Laboratory examinations

The fibrinogen levels were significantly higher in the END group than in the non-END group (3.32 [2.90-3.90] vs. 3.08 [2.60-3.50] g/L, P=0.011). The uric acid levels were significantly lower in the END group than in the non-END group (317 [272-405] vs. 365 [306-439] μmol/L, P=0.024). There were no significant differences between the two groups regarding the levels of WBC, creatinine, FBG, GHbA1c%, TG, T-CH, HDL-C, LDL-C, or homocysteine (Table 2).

Factors associated with END

The logistic regression analysis revealed that higher NIHSS scores at admission (OR=1.086, 95%CI: 1.001-1.179, P=0.047), fibrinogen levels (OR=2.182, 95%CI: 1.286-3.702, P=0.004), and uric acid levels (OR=0.995, 95%CI: 0.990-0.999, P=0.010) were independently associated with END (Table 3). The ROC curve analysis suggested that the sensitivity, specificity, and area under the curve for fibrinogen to discriminate END from non-END were 62.9%, 78.1%, and 0.730 (95% CI: 0.532-0.828, P<0.009), respectively, using a cutoff of 3.47 (Table 4 and Figure 1).

DISCUSSION

This study aimed to evaluate the predictive value of fibrinogen levels at admission for END in patients with LAA stroke without reperfusion therapy. The results suggest that patients with LAA stroke without reperfusion therapy and higher fibrinogen levels at admission were more likely to present END status. These results support that a hypercoagulable state is a crucial determinant of the prognosis of LAA stroke and could help the management of LAA stroke by helping identify patients at higher risk of poor outcomes.

Globally, stroke remained the second-leading cause of death and the third-leading cause of disability in 2019.[5] Atherosclerotic LVD, most commonly in the proximal cervical internal carotid arteries, is the most common mechanism of stroke.[23] Atherosclerosis involves the development of fibrofatty lesions in the artery wall; atherosclerosis is the primary cause

Table 2: Comparison of laboratory tests between the END and Non-END groups

Clinical characteristic	Total (n=179)	END (n=42)	Non-END (n=137)	P
WBC ($\times 10^9$/L), median (IQR)	7.41 (6.18-9.30)	8.31 (6.0-12.7)	7.26 (6.2-9.0)	0.078
Fibrinogen (g/L), median (IQR)	3.14 (2.66-3.60)	3.32 (2.90-3.90)	3.08 (2.60-3.50)	0.011*
Creatinine (μmol/L), median (IQR)	75 (64-87)	75 (66-88)	75 (64-87)	0.980
Uric acid (μmol/L), median (IQR)	350 (298-422)	317 (272-405)	365 (306-439)	0.024*
FBG (mmol/L), median (IQR)	5.60 (4.90-7.40)	5.60 (5.1-7.8)	5.60 (4.8-7.3)	0.314
HbA1c (%), median (IQR)	5.80 (5.50-7.00)	5.95 (5.50-7.60)	5.70 (5.40-6.80)	0.097
TG (mmol/L), median (IQR)	1.43 (1.08-1.90)	1.46 (1.10-1.90)	1.42 (1.10-1.90)	0.781
T-CH (mmol/L), median (IQR)	5.10 (4.37-5.93)	5.50 (4.60-6.10)	4.98 (4.30-5.80)	0.150
HDL-C (mmol/L), median (IQR)	1.04 (0.90-1.22)	1.03 (0.90-1.30)	1.04 (0.90-1.20)	0.989
LDL-C (mmol/L), median (IQR)	3.07 (2.47-3.60)	3.29 (2.40-3.90)	3.01 (2.50-3.60)	0.189
Homocysteine (μmol/L), median (IQR)	11.18 (9.43-14.58)	11.04 (9.80-15.00)	11.19 (9.30-14.70)	0.809

* P<0.05.

END: early neurological deterioration; IQR: interquartile range; WBC: white blood cell count; FBG: fasting blood glucose; HbA1c: glycated hemoglobin; TG: triglyceride; T-CH: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

Table 3: Logistic regression analysis of factors associated with END

Variable	OR (95%CI)	P
Hypertension		
No	Reference	
Yes	0.442 (0.186-1.052)	0.065
Statin use		
No	Reference	
Yes	0.167 (0.028-0.982)	0.051
NIHSS at admission	1.086 (1.001-1.179)	0.047*
Fibrinogen	2.182 (1.286-3.702)	0.004*
Uric acid	0.995 (0.990-0.999)	0.010*

END: early neurological deterioration; OR: odds ratio; CI: confidence interval; NIHSS: National Institutes for Health Stroke Scale.

Table 4: The receiver operating characteristic curve of factors in distinguishing END

Variable	AUC	95%CI	P	Sensitivity	Specificity	Cutoff
NIHSS at admission	0.619	0.522-0.716	0.016	0.452	0.730	5.000
Fibrinogen	0.730	0.532-0.828	0.009	0.629	0.781	3.470
Uric acid	0.385	0.286-0.483	0.022	0.976	0.015	146

END: early neurological deterioration; AUC: area under the curve; CI: confidence interval; NIHSS: National Institutes for Health Stroke Scale.

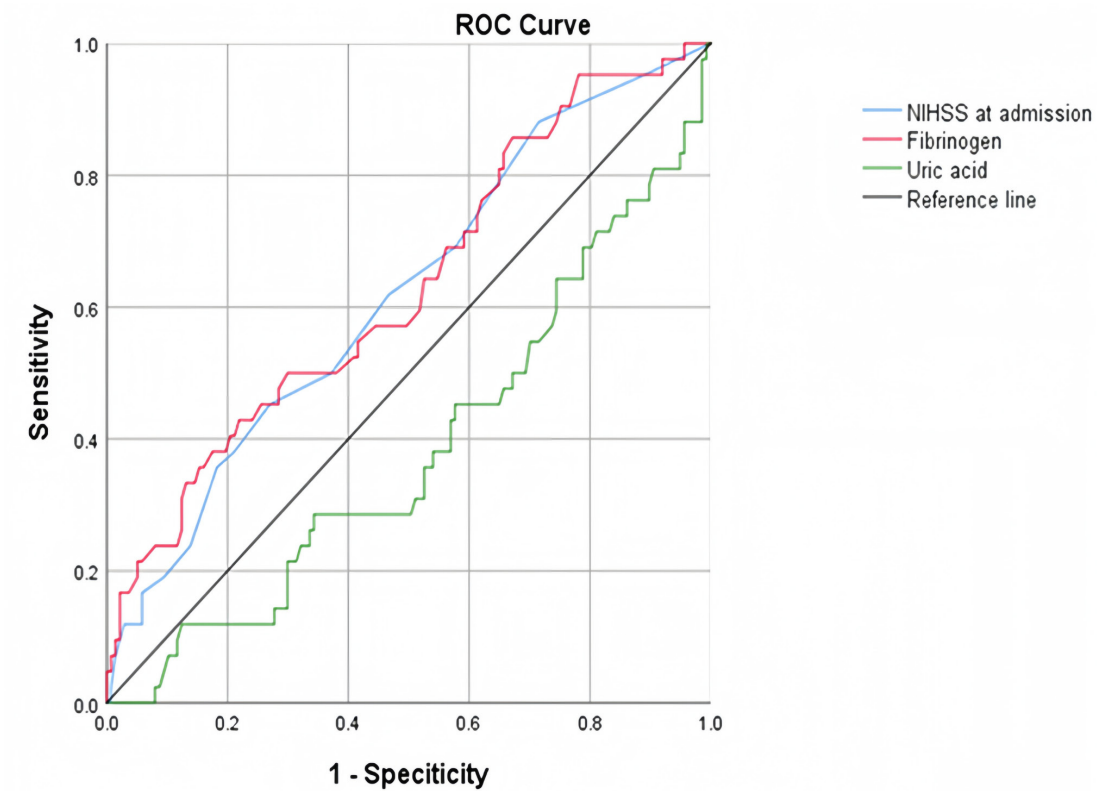

Figure 1. Receiver operating characteristic curve of factors in distinguishing early neurological deterioration.

of ischemia-related morbidity and mortality all over the world.[24] Acute events (such as myocardial infarctions and ischemic strokes) that complicate atherosclerosis arise from thrombosis or the formation of blood clots consequent to the physical disruption of atherosclerotic plaques that expose the highly thrombotic necrotic core of atherosclerotic plaques.[25] LAA is associated with the poorest outcomes among patients with ischemic stroke; the number/importance and stability of the stenotic lesions play important roles in prognosis.[13,26] Traditional prognostic factors for the progression of ischemic stroke included high blood pressure (BP), high glycemia, and ischemic lesions in the carotid artery or basilar artery branch territories.[27] Reperfusion therapy is currently the most effective treatment for this type of stroke, but it requires rapid reperfusion with intravenous thrombolysis and endovascular thrombectomy, and the time window is narrow.[23] Furthermore, intravenous thrombolysis and endovascular thrombectomy are relatively costly therapies, and patients in developing countries might be unable to afford them.[28] Besides obvious causes such as lack of reperfusion, procedural complications, or parenchymal hemorrhage, the occurrence of END remains unexplained in most cases.[29] Thrombotic factors such as fibrinogen are associated with a higher risk of atherosclerotic cardiovascular disease (ASCVD) events, while fibrinolytic factors such as plasminogen are associated with a lower risk of ASCVD events.[30] Atherosclerotic stenosis severity is significantly associated with increased fibrinogen levels in patients with stroke.[31] Recently, a study from the China National Stroke Registry III showed that after adjusting for all confounding risk factors, high baseline fibrinogen levels were associated with poor functional outcomes and dependence for the activities of daily living.[32] Nevertheless, there are limited data on the relationship between END and fibrinogen levels in the first onset of acute stroke with LAA and without reperfusion therapy.

The present study found that the END group had higher proportions of patients with a history of hypertension, higher admission NIHSS scores, and a lower proportion of statin use, but without differences in other traditional cardiovascular risk factors such as age, sex, smoking, diabetes mellitus, hyperlipidemia, prior TIA/stroke, family history of cardiovascular diseases, blood pressure, blood lipids, HbA1c, or antithrombotic, antihypertensive, or antidiabetic medication. In addition, the END group showed higher fibrinogen and lower uric acid levels. The logistic regression analysis revealed that higher NIHSS scores at admission, fibrinogen levels, and uric acid levels were independently associated with END. Fibrinogen plays crucial roles in hemostasis, platelet aggregation, and cell interactions.[16] Fibrinogen levels are a key determinant of blood viscosity.[16] Patients with high fibrinogen levels have a high risk of stroke risk and a poorer prognosis after stroke.[18,19] Hyperfibrinogenemia might directly induce a higher END frequency in LAA stroke through the activation of the coagulation cascade. The final stage of that cascade is the formation of fibrin clots.[16] Fibrin deposition participates in the formation of atherosclerosis plaques.[33] Tanne *et al*.[34] reported that high fibrinogen levels after rt-PA therapy were associated with a higher 90-day mortality risk. However, Marti-Fabregas *et al*.[35] reported that admission fibrinogen levels were not associated with mRS >2 at 3 months, reflecting some inconsistency in the studies.

Still, Li *et al*.[15] reported that high fibrinogen was independently associated with poor outcomes shortly after rt-PA. Their result revealed that fibrinogen >2.69 g/L predicts a poor outcome within 14 days after stroke onset. However, most patients cannot receive reperfusion therapy at the early stage of stroke. Therefore, it is important to identify the risk factors of END in patients with LAA stroke without reperfusion therapy. The present study suggests that fibrinogen is associated with END in patients with LAA stroke without reperfusion therapy. The results might suggest that fibrinogen-reducing therapy could be a treatment option for patients with LAA stroke and hyperfibrinogenemia who have not received reperfusion therapy at admission. Studies will have to examine that point specifically.

This study had some limitations. First, selection and information biases cannot be excluded because this was a retrospective, single-center study. Second, the sample size was small, and the analysis may have been underpowered to detect some real differences between groups. Third, the fibrinogen levels and other laboratory indexes were only measured at admission, and dynamic changes in these parameters during hospitalization could not be assessed. Finally, the study period was January 2018 to December 2018, and more recent data are not available. Nevertheless, prospective studies with larger sample sizes and available laboratory indexes at multiple time points before and during hospitalization would help identify the association between fibrinogen and END in

patients with LAA stroke without reperfusion therapy. Of note, the patients with LAA included in the present study had relatively low NIHSS scores, mainly because this study included patients with LAA stroke who did not undergo vascular recanalization treatment, while patients with higher NIHSS scores usually received such treatments. Therefore, more severe patients were not included in the study population.

In conclusion, END in patients with LAA stroke without reperfusion therapy is associated with a higher NIHSS score and fibrinogen levels at admission and lower uric acid levels. These data might prove useful for predicting and preventing END in patients with LAA stroke without reperfusion therapy. Further studies are needed to characterize the mechanisms underlying the development of END in patients with LAA stroke without reperfusion therapy and to identify ideal management strategies in these patients.

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DISCLOSURES

Availability of data: The data that support the findings of this study are available from the corresponding author.

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Conflict of interests: None

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