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Digestive and urologic hemorrhage after intravenous thrombolysis for acute ischemic stroke: Data from a Chinese stroke center

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Abstract

Objective: Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) is considered the most effective treatment method for AIS; however, it is associated with a risk of hemorrhage. We analyzed the risk factors for digestive and urologic hemorrhage during rt-PA therapy.

Methods: We retrospectively analyzed patients with AIS who underwent intravenous thrombolysis with rt-PA during a 5-year period in a Chinese stroke center. Data on the demographics, medical history, laboratory test results, and clinical outcomes were collected.

Results: 338 patients with AIS were eligible and included. Logistic regression multivariate analysis showed that gastric catheter was significantly correlated with digestive hemorrhage, while age and urinary catheter were significantly correlated with urologic hemorrhage. Most hemorrhagic events were associated with catheterization after 1 to 24 hours of rt-PA therapy.

Conclusions: In summary, gastric and urinary catheters were correlated with digestive and urologic hemorrhage in patients with AIS undergoing rt-PA therapy. Well-designed controlled studies with large samples are required to confirm our findings.

Keywords

Acute ischemic stroke, recombinant tissue plasminogen activator, intravenous thrombolysis, peripheral hemorrhage, risk factor

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Introduction

Acute ischemic stroke (AIS) accounts for about 80% of all types of stroke.[1] The estimated annual incidence of stroke is 0.25% and increases with aging.[2] The clinical syndrome of AIS involves a sudden onset of focal or global disturbance of central nervous system function caused by an interruption in the cerebral circulation. Therefore, the main therapeutic goals for AIS are improvement of the circulation, neuroprotection, and prevention of complications. In addition to endovascular therapy, intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) has been considered the most effective method against AIS,[3] showing significant improvement in the survival rate and quality of life of patients with AIS.

However, intravenous thrombolysis with rt-PA is associated with a risk of hemorrhage. Patients with serious hemorrhage usually have a poor clinical prognosis with a mortality rate of up to 90%.[4] Most studies to date have focused on cerebral hemorrhage as a complication of intravenous thrombolysis. For instance, one study showed that the presence of leukoaraiosis might increase the risk of intracerebral hemorrhage after intravenous thrombolysis in patients with AIS.[5] However, the events associated with peripheral hemorrhage have been rarely discussed despite the fact that these events also affect the survival of patients with AIS who undergo intravenous thrombolysis with rt-PA.[6] In the present study, we analyzed the risk factors for digestive and urologic hemorrhage with the aim of enabling more patients with AIS to gain benefits from rt-PA therapy.

Materials and methods

Study design

We retrospectively analyzed patients with AIS who underwent intravenous thrombolysis with rt-PA during a 5-year period (April 2011–April 2016) in the most well-known stroke center in China (Xuanwu Hospital, Capital Medical University, Beijing). Data on the patients' demographics, medical history, laboratory test results, and clinical outcomes were collected. For intravenous thrombolysis, rt-PA (Boehringer Ingelheim Pharma GmbH, Ingelheim, Germany) was administered at dose of 0.9 mg/kg.

Patient selection

Eligible patients were required to meet the following criteria: age of $\geq$18 years, onset within 4.5 hours, $\geq$1-hour duration of clinical signs related to stroke, no findings of intracranial hemorrhage or early large-area cerebral infarction on brain computed tomography, and provision of informed consent. The exclusion criteria were absence of intact records during rt-PA therapy, performance of arterial thrombolysis after failure of intravenous thrombolysis, and contraindications for rt-PA therapy.

Data collection

We used an electrocardiogram monitor (IntelliVue MP70; Philips Healthcare, USA) to collect the patients' vital signs. The registered clinical data included sex, age, vital signs, height, weight, body mass index, thrombolysis time window, drug administration, and history of hypertension, diabetes, hyperlipidemia, smoking, drinking, coronary heart disease, atrial fibrillation, stroke, transient ischemic attack, peptic ulcer, surgery, and trauma/falls. Twenty-five laboratory parameters were measured from routine blood, biochemical, and coagulation tests, and brain computed tomography scans were performed. All patients were evaluated using the National Institutes of Health Stroke Scale (NIHSS) and activities of daily living (ADL) scale.

Study outcomes

Peripheral hemorrhage such as digestive and urologic hemorrhage occurring within 36 hours of intravenous thrombolysis were the main outcomes in the present study. The diagnosis of digestive hemorrhage was dependent on gastric juice and feces test results, while the presence of positive red blood cells on routine urinalysis was necessary for a diagnosis of urologic hemorrhage.

Statistical analysis

We used EpiData 3.1 (EpiData, Odense, Denmark) to set up the database with double-personnel data entry and SPSS v.18.0 (SPSS Inc., Chicago, IL, USA) to analyze the data. For all tests, differences were considered statistically significant at a p value of <0.05.

Ethical considerations

This study was approved by the ethics committee of Capital Medical University. Prior to entering the study, all patients were informed of the study procedures.

Results

In total, 338 patients with AIS were eligible and included in the study. Of these patients,

Table 1. Comparison of clinical data between patients with and without digestive hemorrhage

	No hemorrhage (n = 320)	Hemorrhage (n = 18)	t/χ^2	p
Age in years	60.02 ± 11.59	65.33 ± 8.32	t = −1.918	0.056
Sex			$\chi^2 = 2.718$	0.099
Male	227 (70.9)	16 (88.9)		
Female	93 (29.1)	2 (11.1)		
Body mass index, kg/m^2	25.55 ± 3.41	25.93 ± 2.95	t = −0.461	0.645
Baseline SBP, mmHg	147.27 ± 20.75	158.72 ± 24.42	t = −2.257	0.025
Baseline DBP, mmHg	82.91 ± 12.81	87.33 ± 11.822	t = −1.430	0.154
Hypertension	194 (60.6)	12 (66.7)	$\chi^2 = 0.609$	0.805
Diabetes	105 (32.8)	3 (16.7)	$\chi^2 = 2.059$	0.357
Hyperlipidemia	51 (15.9)	1 (5.6)	$\chi^2 = 1.411$	0.235
Coronary heart disease	48 (15.0)	5 (27.8)	$\chi^2 = 2.104$	0.147
Atrial fibrillation	44 (13.8)	5 (27.8)	$\chi^2 = 2.705$	0.100
Stroke	56 (17.5)	6 (33.3)	$\chi^2 = 2.852$	0.091
Peptic ulcer	8 (2.5)	0 (0.0)	$\chi^2 = 0.461$	0.497
History of falls	12 (3.8)	2 (11.1)	$\chi^2 = 2.326$	0.127
Smoking	168 (52.5)	11 (61.1)	$\chi^2 = 0.507$	0.476
Drinking	140 (43.8)	11 (61.1)	$\chi^2 = 2.078$	0.149
Thrombolysis time window	3.48 ± 1.82	3.46 ± 1.15	t = 0.027	0.979
NIHSS score before rt-PA	7.41 ± 5.42	10.94 ± 4.41	t = −2.715	0.007
ADL score before rt-PA	43.88 ± 20.31	26.11 ± 10.23	t = 25.32	0.000
Aspirin 24 hours after rt-PA	226 (70.6)	7 (38.9)	$\chi^2 = 8.015$	0.005
Clopidogrel 24 hours after rt-PA	165 (51.6)	7 (38.9)	$\chi^2 = 1.095$	0.295
LMH after rt-PA	45 (14.1)	3 (16.7)	$\chi^2 = 0.095$	0.758
Aspirin and clopidogrel 24 hours after rt-PA	107 (33.4)	3 (16.7)	$\chi^2 = 0.095$	0.002

Data are presented as n (%) or mean ± standard deviation unless otherwise indicated.
ADL: activities of daily living; DBP: diastolic blood pressure; LMH: low-molecular-weight heparin; NIHSS: National Institutes of Health Stroke Scale; rt-PA: recombinant tissue plasminogen activator; SBP: systolic blood pressure.

18 (5.3%) developed digestive hemorrhage and 24 (7.1%) developed urologic hemorrhage within 36 hours of intravenous thrombolysis.

In general, the systolic blood pressure at baseline ($t = -2.257$, $p = 0.025$), NIHSS score ($t = -2.715$, $p = 0.007$) and ADL score ($t = 25.32$, $p = 0.000$) before rt-PA therapy, and administration of a single aspirin dose ($t = 8.015$, $p = 0.005$) or aspirin combined with clopidogrel ($t = 0.095$, $p = 0.002$) within 24 hours after rt-PA therapy were significantly different between patients with and without digestive hemorrhage (Table 1). The red blood cell count ($t = 2.169$, $p = 0.031$) and blood urea nitrogen concentration ($t = -1.994$, $p = 0.047$) were the distinguishable tests (Table 2). Furthermore, the presence of a gastric catheter ($\chi^2 = 63.224$, $p = 0.000$) was an important risk factor for digestive hemorrhage (Table 3). Multivariate logistic regression analysis of the above-mentioned possible risk factors showed that only a gastric catheter ($\chi^2 = 11.564$, $p = 0.001$) was significantly correlated with digestive

Table 3. Comparison of gastric catheter between patients with and without digestive hemorrhage

	No hemorrhage (n = 320)	Hemorrhage (n = 18)	χ^2	p
With GC	29 (9.1)	12 (66.7)	63.224	0.000
Without GC	291 (90.9)	6 (33.3)		

Data are presented as n (%) unless otherwise indicated.
GC: gastric catheter.

Table 2. Comparison of laboratory parameters between patients with and without digestive hemorrhage

	No hemorrhage (n = 320)	Hemorrhage (n = 18)	t	p
White blood cell count ($*10^{9/L}$)	7.93 ± 2.20	8.28 ± 2.72	−0.633	0.527
Percentage of neutrophils (%)	64.91 ± 16.28	60.70 ± 27.30	0.648	0.525
Red blood cell count ($*10^{12/L}$)	4.57 ± 0.48	4.31 ± 0.64	2.169	0.031
Hemoglobin (g/L)	140.48 ± 0.82	134.00 ± 20.10	1.786	0.075
Hematocrit (%)	41.15 ± 5.77	39.37 ± 6.00	1.265	0.207
Platelet count ($*10^{9/L}$)	208.21 ± 123.43	199.16 ± 44.59	0.310	0.757
Alanine transaminase (IU/L)	23.14 ± 17.75	31.79 ± 57.28	−0.639	0.531
Aspartate transaminase (IU/L)	26.68 ± 15.39	31.85 ± 19.29	−1.367	0.173
Creatinine (μmol/L)	69.06 ± 16.28	71.78 ± 17.28	−0.689	0.491
Urea nitrogen (mmol/L)	6.12 ± 2.57	7.37 ± 3.17	−1.994	0.047
Glucose (mmol/L)	7.84 ± 3.13	9.22 ± 3.96	−1.793	0.074
Uric acid (μmol/L)	322.68 ± 87.73	360.89 ± 104.07	−1.780	0.076
Triglyceride (mmol/L)	2.26 ± 1.53	3.77 ± 4.70	−1.357	0.192
Cholesterol (mmol/L)	6.55 ± 28.37	5.00 ± 1.58	0.230	0.818
Low-density lipoprotein (mmol/L)	2.87 ± 0.81	2.59 ± 0.79	1.403	0.161
Prothrombin time activity (%)	102.26 ± 14.63	101.40 ± 15.09	0.241	0.810
Prothrombin time, INR	1.01 ± 0.18	1.01 ± 0.10	0.083	0.934
Prothrombin time, s	13.22 ± 1.52	13.27 ± 0.97	−0.138	0.891
Thrombin time, s	17.31 ± 8.29	23.68 ± 27.23	−0.990	0.336
Activated partial thrombin time, s	34.70 ± 3.49	35.38 ± 4.41	−0.795	0.427
Fibrinogen (g/l)	3.45 ± 1.27	3.21 ± 0.68	0.791	0.429
D-dimers (μg/ml)	0.75 ± 0.18	0.73 ± 0.10	0.553	0.581

Data are presented as mean ± standard deviation unless otherwise indicated.
INR: international normalized ratio.

Table 4. Logistic regression analysis of risk factors for digestive hemorrhage

						95% CI	
	B	SE	χ^2 (Wald)	p	OR	Upper limit	Lower limit
ADL score before rt-PA	−0.045	0.026	2.998	0.083	0.956	0.909	1.006
Systolic pressure	0.022	0.013	2.656	0.103	1.022	0.996	1.049
NIHSS score before rt-PA	−0.039	0.062	0.397	0.528	0.962	0.851	1.086
Aspirin after rt-PA	0.354	0.828	0.183	0.669	1.425	0.281	7.224
Aspirin and clopidogrel	0.051	0.833	0.004	0.951	1.052	0.205	5.389
RBC before rt-PA	−0.786	0.538	2.139	0.144	0.456	0.159	1.307
BUN before rt-PA	0.099	0.065	2.264	0.132	1.104	0.971	1.255
Gastric catheter	1.112	0.327	11.564	0.001	3.041	1.602	5.773

Likelihood ratio test = 98.298, Cox and Snell $R^2 = 0.118$, Nagelkerke $R^2 = 0.346$.
ADL: activities of daily living; BUN: blood urea nitrogen; CI: confidence interval; NIHSS: National Institutes of Health Stroke Scale; OR: odds ratio; RBC: red blood cell count; rt-PA: recombinant tissue plasminogen activator; SE: standard error.

Table 5. Comparison of clinical data between patients with and without urologic hemorrhage

	No hemorrhage (n = 314)	Hemorrhage (n = 24)	t/χ^2	p
Age	59.73 ± 11.29	67.79 ± 11.70	t = −3.364	0.001
Sex			$\chi^2 = 0.123$	0.725
Male	225 (71.7)	18 (75.0)		
Female	89 (28.3)	6 (25.0)		
Body mass index, kg/m^2	25.58 ± 3.39	25.41 ± 3.40	t = 0.237	0.813
Baseline SBP, mmHg	147.45 ± 21.05	153.46 ± 21.08	t = −1.348	0.179
Baseline DBP, mmHg	82.95 ± 12.84	85.79 ± 11.94	t = −1.052	0.294
Hypertension	192 (61.1)	14 (58.3)	$\chi^2 = 0.074$	0.785
Diabetes	97 (30.9)	11 (45.8)	$\chi^2 = 2.45$	0.294
Hyperlipidemia	51 (16.2)	1 (4.2)	$\chi^2 = 2.50$	0.114
Coronary heart disease	46 (14.6)	7 (29.2)	$\chi^2 = 3.554$	0.059
Atrial fibrillation	45 (14.3)	4 (16.7)	$\chi^2 = 0.098$	0.754
Stroke	57 (18.2)	5 (20.8)	$\chi^2 = 0.107$	0.744
Peptic ulcer	7 (2.2)	1 (4.2)	$\chi^2 = 0.362$	0.547
History of falls	12 (3.8)	2 (11.1)	$\chi^2 = 1.143$	0.285
Smoking	168 (53.5)	11 (45.8)	$\chi^2 = 0.526$	0.468
Drinking	138 (43.9)	13 (54.2)	$\chi^2 = 0.942$	0.332
Thrombolysis time window	3.43 ± 1.82	4.06 ± 1.23	t = −1.671	0.096
NIHSS score before rt-PA	7.32 ± 5.27	11.29 ± 6.10	t = −3.519	0.000
ADL score before rt-PA	44.04 ± 19.82	28.33 ± 21.15	t = 3.725	0.000
Aspirin 24 hours after rt-PA	220 (70.1)	13 (54.2)	$\chi^2 = 2.631$	0.105
Clopidogrel 24 hours after rt-PA	160 (51.0)	12 (50.0)	$\chi^2 = 0.008$	0.928
LMH after rt-PA	40 (12.7)	8 (33.3)	$\chi^2 = 7.761$	0.005
Aspirin and clopidogrel 24 hours after rt-PA	105 (33.4)	5 (20.8)	$\chi^2 = 1.689$	0.430

Data are presented as n (%) or mean ± standard deviation unless otherwise indicated.
ADL: activities of daily living; DBP: diastolic blood pressure; LMH: low-molecular-weight heparin; NIHSS: National Institutes of Health Stroke Scale; rt-PA: recombinant tissue plasminogen activator; SBP: systolic blood pressure.

hemorrhage (likelihood ratio test = 98.298, Cox and Snell $R^2 = 0.118$, Nagelkerke $R^2 = 0.346$) (Table 4).

The significant risk factors for urologic hemorrhage were age ($t = -3.364$, $p = 0.001$), the NIHSS score ($t = -3.519$, $p = 0.000$), and the ADL score ($t = 3.725$, $p = 0.000$) before rt-PA therapy; administration of low-molecular-weight heparin ($\chi^2 = 7.761$, $p = 0.005$) after rt-PA therapy; and the triglyceride concentration ($t = 2.059$, $p = 0.040$), prothrombin time activity ($t = 2.451$, $p = 0.015$), and presence of a urinary catheter ($\chi^2 = 26.27$, $p = 0.000$) (Tables 5–7). Multivariate logistic regression analysis of the above-mentioned possible risk factors showed that age ($\chi^2 = 4.422$, $p = 0.035$) and a urinary catheter ($\chi^2 = 7.868$, $p = 0.005$) were significantly correlated with urologic hemorrhage (likelihood ratio test = 132.044, Cox and Snell $R^2 = 0.115$, Nagelkerke $R^2 = 0.286$) (Table 8).

With respect to the relationship between the time of catheterization and the development of peripheral hemorrhage, most

Table 7. Comparison of urinary catheter between patients with and without urologic hemorrhage

	No hemorrhage (n = 314)	Hemorrhage (n = 24)	χ^2	p
With UC	37 (11.8)	12 (50.0)	26.27	0.000
Without UC	277 (88.2)	12 (50.0)		

Data are presented as n (%).
UC: urinary catheter.

Table 6. Comparison of laboratory parameters between patients with and without urologic hemorrhage

	No hemorrhage (n = 320)	Hemorrhage (n = 24)	t	p
White blood cell count	8.00 ± 2.25	7.35 ± 1.71	1.380	0.168
Percentage of neutrophils	64.65 ± 16.71	65.20 ± 21.00	−0.151	0.880
Red blood cell count	4.56 ± 0.49	4.47 ± 0.52	0.870	0.385
Hemoglobin	140.23 ± 15.02	138.88 ± 15.43	0.424	0.672
Hematocrit	41.01 ± 5.85	41.55 ± 4.87	−0.438	0.662
Platelet count	208.75 ± 123.72	194.38 ± 65.65	0.563	0.574
Alanine transaminase	23.82 ± 21.72	20.67 ± 20.57	0.688	0.492
Aspartate transaminase	27.35 ± 16.08	21.71 ± 5.82	1.710	0.088
Creatinine	69.24 ± 16.08	68.75 ± 19.55	0.119	0.906
Urea nitrogen	6.19 ± 2.66	6.05 ± 1.94	0.252	0.801
Glucose	7.87 ± 3.10	8.48 ± 4.19	−0.701	0.490
Uric acid	325.55 ± 89.60	313.67 ± 80.25	0.631	0.529
Triglyceride	2.40 ± 1.89	1.59 ± 1.02	2.059	0.040
Cholesterol	6.62 ± 28.64	4.46 ± 1.18	0.368	0.713
Low-density lipoprotein	2.86 ± 0.79	2.82 ± 1.14	0.228	0.820
Prothrombin time activity	102.75 ± 14.56	95.21 ± 14.06	2.451	0.015
Prothrombin time, INR	1.01 ± 0.18	1.01 ± 0.10	−0.949	0.343
Prothrombin time, s	13.19 ± 1.53	13.64 ± 0.98	−1.399	0.163
Thrombin time, s	17.69 ± 10.60	17.14 ± 1.07	0.254	0.800
Activated partial thrombin time, s	34.58 ± 3.33	36.75 ± 5.34	−1.961	0.061
Fibrinogen	3.43 ± 1.27	3.53 ± 0.89	−0.357	0.721
D-dimers	0.75 ± 0.18	0.75 ± 0.00	0.000	1.000

Data are presented as mean ± standard deviation unless otherwise indicated.
INR: international normalized ratio.

Table 8. Logistic regression analysis of risk factors for urologic hemorrhage

						95% CI	
	B	SE	χ^2 (Wald)	p	OR	Upper limit	Lower limit
Age	0.048	0.023	4.422	0.035	1.050	1.003	1.098
ADL score before rt-PA	−0.030	0.019	2.422	0.120	0.971	0.935	1.008
NIHSS score before rt-PA	0.003	0.048	0.004	0.949	1.003	0.914	1.101
LMH after rt-PA	0.694	0.533	1.696	0.193	2.002	0.704	5.694
Triglycerides	−0.391	0.268	2.140	0.143	0.676	0.400	1.142
PTA	−0.017	0.016	1.038	0.308	0.984	0.953	1.015
Urinary catheter	0.723	0.258	7.868	0.005	2.061	1.243	3.415

Likelihood ratio test = 132.044, Cox and Snell $R^2 = 0.115$, Nagelkerke $R^2 = 0.286$.
ADL: activities of daily living; BUN: blood urea nitrogen; CI: confidence interval; LMH: low-molecular-weight heparin, NIHSS: National Institutes of Health Stroke Scale; OR: odds ratio; rt-PA: recombinant tissue plasminogen activator; PTA: prothrombin time activity; SE: standard error.

Table 9. Analysis of the timepoint of catheterization and peripheral hemorrhage.

	Gastric catheter	Urinary catheter
Total cases of hemorrhage	12	12
CTR before rt-PA therapy	1 (8.3)	0 (0.0)
CTR after rt-PA therapy		
≤1 h	0 (0.0)	2 (16.7)
1–24 h	9 (75.0)	7 (58.3)
>24 h	2 (16.7)	3 (25.0)

Data are presented as n (%).
rt-PA: recombinant tissue plasminogen activator; CTR: catheterization.

adverse events were related to catheterization after 1 to 24 hours of rt-PA therapy. The proportion was 75.0% (9 of 12 events) among patients with digestive hemorrhage and 58.3% (7 of 12 events) among patients with urologic hemorrhage.

Discussion

At present, rt-PA is the most widely used therapy for intravenous thrombolysis worldwide.[7] Most studies have mainly focused on the development of cerebral hemorrhagic events caused by rt-PA[8]; relatively little is known about the risk factors for peripheral hemorrhage. One study focused on 1044 patients with AIS who underwent intravenous thrombolysis with rt-PA and found that hypertension at baseline was closely correlated with hemorrhagic events.[9] Blood pressure control (systolic blood pressure < 185 mmHg, diastolic blood pressure < 185 mmHg) has been confirmed to be beneficial in preventing hemorrhagic events after rt-PA therapy.[10] The NIHSS score is another important index for predicting hemorrhagic events after rt-PA therapy. An NIHSS score of >25 is generally thought to be a contraindication for rt-PA therapy.[11] Our analyses revealed the following risk factors: the systolic blood pressure at baseline, the NIHSS and ADL scores before rt-PA therapy, and administration of a single aspirin dose or aspirin combined with clopidogrel within 24 hours after rt-PA therapy. Various drugs such as cortisol, aspirin, and nonsteroidal anti-inflammatory drugs are known to potentially result in stomach ulcers and bleeding.[12]

We identified the following risk factors for urologic hemorrhage: age, the NIHSS and ADL scores before rt-PA therapy, use of low-molecular-weight heparin after rt-PA

therapy, the triglyceride concentration, and the prothrombin time activity. Low-molecular-weight heparin is generally believed to have satisfactory safety and a low risk of bleeding.[13] However, more attention should be given to patients undergoing rt-PA therapy, especially when they have other risk factors such as high age. No significant differences were found in sex, although this can likely be attributed to the small sample size. Male patients are usually more vulnerable to hemorrhagic events.[14] Potential selection bias could be another reason. For instance, fewer older patients underwent rt-PA therapy because of the higher risk with age. The male:female ratio was 2.6:1.0, which meant male-dominant sample. Solutions to these problems might include expansion of the sample size, inclusion of multiple populations, and proper randomization. The multivariate logistic regression analysis showed that catheterization was an independent risk factor for patients with AIS undergoing rt-PA therapy. Impairments during catheterization might give rise to hemorrhagic events.

In summary, gastric and urinary catheterization were respectively correlated with digestive and urologic hemorrhage in patients with AIS undergoing rt-PA therapy. Well-designed controlled studies with large samples are required to confirm our findings. Classification of bleeding as minor, moderate, and severe according to the Global Use of Strategies To Open coronary arteries (GUSTO) criteria should also be considered.[15]

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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