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

Hong Chang¹,* , Xiaojuan Wang¹, Xin Yang², Haiqing Song¹, Yuchen Qiao¹ and Jia Liu¹

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

Date received: 12 September 2016; accepted: 5 December 2016
**Introduction**

Acute ischemic stroke (AIS) accounts for about 80% of all types of stroke. The estimated annual incidence of stroke is 0.25% and increases with aging. 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, 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%. 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. 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. 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 ≥18 years, onset within 4.5 hours, ≥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/χ² | p |
|--------------------------|------------------|-----|---|
| Age in years | 60.02 ± 11.59 | 65.33 ± 8.32 | t = -1.918 | 0.056 |
| Sex | χ² = 2.718 | 0.099 |
| Male | 227 (70.9) | 16 (88.9) |
| Female | 93 (29.1) | 2 (11.1) |
| Body mass index, kg/m² | 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) | χ² = 0.609 | 0.805 |
| Diabetes | 105 (32.8) | 3 (16.7) | χ² = 2.059 | 0.357 |
| Hyperlipidemia | 51 (15.9) | 1 (5.6) | χ² = 1.411 | 0.235 |
| Coronary heart disease | 48 (15.0) | 5 (27.8) | χ² = 2.104 | 0.147 |
| Atrial fibrillation | 44 (13.8) | 5 (27.8) | χ² = 2.705 | 0.100 |
| Stroke | 56 (17.5) | 6 (33.3) | χ² = 2.852 | 0.091 |
| Peptic ulcer | 8 (2.5) | 0 (0.0) | χ² = 0.461 | 0.497 |
| History of falls | 12 (3.8) | 2 (11.1) | χ² = 2.326 | 0.127 |
| Smoking | 168 (52.5) | 11 (61.1) | χ² = 0.507 | 0.476 |
| Drinking | 140 (43.8) | 11 (61.1) | χ² = 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) | χ² = 8.015 | 0.005 |
| Clopidogrel 24 hours after rt-PA | 165 (51.6) | 7 (38.9) | χ² = 1.095 | 0.295 |
| LMH after rt-PA | 45 (14.1) | 3 (16.7) | χ² = 0.095 | 0.758 |
| Aspirin and clopidogrel 24 hours after rt-PA | 107 (33.4) | 3 (16.7) | χ² = 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 ($t = 63.224, p = 0.000$) 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 ($x^2 = 11.564, p = 0.001$) was significantly correlated with digestive

### 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 ($\times 10^{9}/L$) | 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 ($\times 10^{12}/L$) | 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 ($\times 10^{9}/L$) | 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

|                          | B      | SE     | $\chi^2$ (Wald) | p     | OR    | 95% CI          |
|--------------------------|--------|--------|-----------------|-------|-------|-----------------|
| 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) | $t$/$\chi^2$ | 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/m² | 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 ($t = -7.761$, $p = 0.005$) 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 ($t = 26.27$, $p = 0.000$) (Tables 5–7).

Multivariate logistic regression analysis of the above-mentioned possible risk factors showed that age ($t = 4.422$, $p = 0.035$) and a urinary catheter ($t = 7.868$, $p = 0.005$) 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) | $\chi^2$ | 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.
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. Most studies have mainly focused on the development of cerebral hemorrhagic events caused by rt-PA, 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. 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. 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. 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.

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, and control of blood pressure within 24 hours after rt-PA therapy.
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. 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. 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.

Declaration of conflicting interests
The authors declare that there is no conflict of interest.

Funding
This research was supported Beijing Municipal Administration of Hospitals Youth Program (QML20150805), as well as the Biological Medicine and Life Sciences Innovation Project (Z151100003915088), Beijing Science and Technology Commission.

References
1. Liu J and Wang LN. Gamma aminobutyric acid (GABA) receptor agonists for acute stroke. Cochrane Database Syst Rev 2014; CD009622.
2. Liu J and Wang LN. Peroxisome proliferator-activated receptor gamma agonists for preventing recurrent stroke and other vascular events in patients with stroke or transient ischaemic attack. Cochrane Database Syst Rev 2015; CD010693.
3. Tissue plasminogen activator for acute ischaemic stroke. The national institute of neurological disorders and stroke rt-PA stroke study group. N Engl J Med 1995; 333: 1581–1587.
4. Wardlaw JM, Murray V, Berge E, et al. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev 2014; CD000213.
5. Charidimou A, Pasi M, Fiorelli M, et al. Leukoaraiosis, cerebral hemorrhage, and outcome after intravenous thrombolysis for acute ischemic stroke: a meta-analysis (v1). Stroke 2016; 47: 2364–2372.
6. Brownlee WJ, Wu TY, Van Dijck SA, et al. Upper limb compartment syndrome: an unusual complication of stroke thrombolysis. J Clin Neurosci 2014; 21: 880–882.
7. Demaerschalk BM, Kleindorfer DO, Adeoye OM, et al. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke: a statement for healthcare professionals from the american heart association/american stroke association. Stroke 2016; 47: 581–641.
8. Rodrigues FB, Neves JB, Caldeira D, et al. Endovascular treatment versus medical care alone for ischaemic stroke: systematic review and meta-analysis. BMJ 2016; 353: i1754.
9. Hsia AW, Edwards DF, Morgenstern LB, et al. Racial disparities in tissue plasminogen activator treatment rate for stroke: a population-based study. Stroke 2011; 42: 2217–2221.
10. Li C, Wang Y, Chen Y, et al. Optimal blood pressure levels in patients undergoing intravenous thrombolysis for AIS. *Minerva Med* 2015; 106: 255–258.

11. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. The NINDS t-PA stroke study group. *Stroke* 1997; 28: 2109–2118.

12. Alvarez-Sabin J, Quintana M, Santamarina E, et al. Triflusal and aspirin in the secondary prevention of atherothrombotic ischemic stroke: a very long-term follow-up. *Cerebrovasc Dis* 2014; 37: 181–187.

13. Holzheimer RG. Low-molecular-weight heparin (LMWH) in the treatment of thrombosis. *Eur J Med Res* 2004; 9: 225–239.

14. Cuzick J, Thorat MA, Bosetti C, et al. Estimates of benefits and harms of prophylactic use of aspirin in the general population. *Ann Oncol* 2015; 26: 47–57.

15. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. *N Engl J Med* 1993; 329: 673–682.