Boehringer Ingelheim

Protocol for non-interventional studies based on existing data

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Title:	Temporal trends of thrombolysis treatment in Chinese acute ischemic stroke (AIS) patients from 2007-2017: analysis of China National Stroke Registry (CNSR) I, II, and III
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Date of last version of protocol:	12 Mar 2020
PASS:	No
EU PAS register number:	EUPAS33970
Active substance:	Alteplase
Medicinal product:	Actilyse
Product reference:	Not applicable
Procedure number:	Not applicable
Joint PASS:	No
Research question and objectives:	Primary objectives: • To investigate the temporal changes in the proportion of intravenous recombinant plasminogen activator (IV-rtPA) treatment from 2007 to 2017 among intravenous thrombolytics (IVT)-eligible patients and overall AIS patients in China; • To investigate the temporal changes in IV-rtPA treatment time intervals from 2007 to 2017 among IV-rtPA-treated patients in China. Secondary objectives: • To describe the demographic and clinical characteristics of the IV-rtPA-treated patients, IVT-eligible patients and the overall AIS patients from the CNSR I to III.

Country(-ies) of study:	China
Author:	[redacted]
Marketing authorisation holder(s):	[redacted]
MAH contact person:	Not applicable
In case of PASS, add: **<EU-QPPV:>**	Not applicable
In case of PASS, add: **<Signature of EU-QPPV:>**	Not applicable
Date:	17 Apr 2020
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2. LIST OF ABBREVIATIONS

ADRs	Adverse Drug Reactions
AEs	Adverse Events
AIS	Acute Ischemic Stroke
BI	Boehringer Ingelheim
CI	Confidence Interval
CRC	Clinical Research Coordinators
CRF	Case Report Form
CROs	Contract Research Organizations
CNSR	China National Stroke Registry
CT	Computed Tomography
DSMB	Data Safety and Management Board
DTN	Door to Needle
ECASS	European Cooperative Acute Stroke Study
EDC	Electronic Data Capture
[redacted]	[redacted]
ESOC	European Stroke Organization Conference
GPP	Good Pharmacoepidemiology Practices
H	Hours
ICFs	Informed Consent Forms
ICH	Intracranial Hemorrhage
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IS	Ischemic Stroke
IV-rtPA	Intravenous Recombinant Plasminogen Activator
IVT	Intravenous Thrombolytics
Min	Minutes
MOH	Ministry of Health
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
NCRC-ND	National Clinical Research Center for Neurological Diseases
NIHSS	National Institutes of Health Stroke Scale
PRF	Paper-based Registry Forms

SAH	SubArachnoid Hemorrhage
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOPs	Standard Operation Procedures
TIA	Transient Ischemic Attack

3. RESPONSIBLE PARTIES

BI Contact Person:

[redacted]
Address: [redacted]
[redacted]
Contact details: [redacted]

Principal Investigator:

[redacted]
Address: [redacted]
[redacted]
Contact details: [redacted]

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Actilyse			
Name of active ingredient: Alteplase			
Protocol date: 17 Apr 2020	**Study number:** 0135-0343	**Version/Revision:** 1.1	**Version/Revision date:** 12 Mar 2020
Title of study:	Temporal trends of thrombolysis treatment in Chinese acute ischemic stroke patients (AIS) from 2007-2017: analysis of China National Stroke Registry (CNSR) I, II, and III		
Rationale and background:	Based on the conclusion from the European Cooperative Acute Stroke Study (ECASS) III study, the Chinese treatment guideline for AIS was updated in 2010, with intravenous recombinant plasminogen activator (IV-rtPA) treatment recommendation time window extended from within 3h of symptom onset to 4.5h. In addition, efforts have been taken by the government and academic societies to develop stroke centers and stroke care quality control networks. In order to understand the impact of these efforts on the clinical practices for AIS treatment in China, we plan to evaluate the 10-year temporal changes from 2007-2017, in the IV-rtPA treatment proportion and treatment time intervals of AIS patients by using the CNSR I, II, and III. In addition, the demographic and clinical characteristics of the AIS patients will be described.		
Research question and objectives:	Primary objectives: • To investigate the temporal changes in the proportion of intravenous recombinant plasminogen activator (IV-rtPA) treatment from 2007 to 2017 among intravenous thrombolytics (IVT)-eligible patients and overall AIS patients in China; • To investigate the temporal changes in IV-rtPA treatment time intervals from 2007 to 2017 among IV-rtPA-treated patients in China. Secondary objectives: • To describe the demographic and clinical characteristics of the IV-rtPA-treated patients, IVT-eligible patients and the overall AIS patients from the CNSR I to III.		
Study design:	This is a non-interventional study based on existing data from the CNSR.		

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Protocol date: 17 Apr 2020	**Study number:** 0135-0343	**Version/Revision:** 1.1	**Version/Revision date:** 12 Mar 2020

Population:

All eligible patients from the CNSR I to III will be included. Patient groups include the overall AIS patients (patient group A), IVT-eligible patients (patient groups B and B'), and IV-rtPA-treated patients (patient groups C and C').

The in- and exclusion criteria for the reporting groups are listed below:

1) All AIS patients (patient group A)

1. Inclusion criteria:
   - (1) Aged 18-80 years
   - (2) Diagnosed with AIS on admission
2. Exclusion criteria:
   - (1) Missing baseline data including age and gender
   - (2) Diagnosed with intracranial intracranial hemorrhage (ICH), Transient Ischemic Attack (TIA), subarachnoid hemorrhage (SAH), or unspecific stroke
   - (3) Arrived at hospital after 7 days of symptom onset

2) IVT-eligible patients (patient groups B and B')

1. Inclusion criteria:
   - (1) Met the in- and exclusion criteria of "all AIS patients"
   - (2) Arrived at hospital within 2h (patient group B) or 3.5h (patient group B') of symptom onset
2. Exclusion criteria:
   - (1) Missing key data including
     - i. symptom onset time (or last known well time);
     - ii. hospital arrival time;
     - iii. whether received IVT treatment or not;
     - iv. the time of IVT treatment.
   - (2) Documented IVT absolute contraindications, according to the case report form (CRF) for each wave of CNSR (please refer to ANNEX 3 for details)

3) IV-rtPA-treated patients (patient groups C and C')

Name of company: Boehringer Ingelheim			
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Protocol date: 17 Apr 2020	**Study number:** 0135-0343	**Version/Revision:** 1.1	**Version/Revision date:** 12 Mar 2020
	1. Inclusion criteria: (1) Met the in- and exclusion criteria of "IVT-eligible patients" (2) Treated with IV-rtPA within 3h (patient group C) or 4.5h (patient group C') of symptom onset 2. Exclusion criteria: (1) Not received IVT (2) Received IVT other than rtPA (3) Treated with IV-rtPA after 3h (patient group C) or 4.5h (patient group C') of symptom onset (4) Received additional treatments with intra-arterial reperfusion or experimental therapies		
Variables and co-variables:	**Primary outcomes:** For all the three waves of CNSR, the following primary outcomes will be assessed: ● Proportion of patients who received IV-rtPA treatment within 3h of symptom onset (patient group C) among 2hr IVT-eligible patients (patient group B); ● Proportion of patients who received IV-rtPA treatment within 4.5h of symptom onset (patient group C') among 3.5h IVT-eligible patients (patient group B'). **Secondary outcomes: the analysis will be performed for each wave of CNSR** Among all AIS patients (patient group A), the following secondary outcomes will be assessed: ● Proportion of patients who arrived at hospital within 2h of symptom onset and who received IV-rtPA treatment within 3h of symptom onset (patient group C); ● Proportion of patients who arrived at hospital within 3.5h of symptom onset and who received IV-rtPA treatment within 4.5h of symptom onset (patient group C'); Among 3h IV-rtPA-treated patients (patient group C), the following secondary outcomes will be assessed: ● The door-to-needle (DTN) time (time between arrival at hospital and the administration of IV-rtPA treatment);		

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- Proportion of patients DTN time ≤ 60 minutes (min);
- Time between symptom onset and arrival at hospital;
- Time between symptom onset and the administration of IV-rtPA treatment.

Among 4.5h IV-rtPA-treated patients (patient group C'), the following secondary outcomes will be assessed:

- The DTN time;
- Proportion of patients DTN time ≤ 60 min;
- Time between symptom onset and arrival at hospital;
- Time between symptom onset and the administration of IV-rtPA treatment.

[redacted]

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	[redacted]		

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12 Mar 2020</td></tr>
<tr><td>Data sources:</td><td colspan="3">CNSR I, II, and III</td></tr>
<tr><td>Study size:</td><td colspan="3">It was estimated that in CNSR I, II, and III, the number of total AIS patients is 14704, 19604, and 15204, respectively.

Assuming the IV-rtPA-treated among IVT-eligible patients in CNSR I, II, and III are 4%, 5%, and 28% with the 95% confidence interval (CI) for each wave as below, then which can be distinguished with current study size.
<table>
<tr><td>CNSR</td><td>Wave I</td><td>Wave II</td><td>Wave III</td></tr>
<tr><td>Assumed IV-rtPA proportion among eligible patients % (95% CI)</td><td>4%
(3.7-4.3%)</td><td>5%
(4.7-5.3%)</td><td>28%
(27.3-28.7%)</td></tr>
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<tr><td>Data analysis:</td><td colspan="3">The study is descriptive in nature. For continuous data, descriptive statistics (number of patients, mean, standard deviation [SD], minimum, median, interquartile range, and maximum) will be presented. Categorical data will be presented as frequency and proportion with 95% CI as appropriate.

[redacted]</td></tr>
<tr><td>Milestones:</td><td colspan="3">Feasibility assessment: Jun 2019
Protocol finalization: Dec 2019
Statistical and epidemiological analysis plan: Mar 2020
Start of data collection: NA
End of data collection: NA
Statistical and epidemiological analysis report finalization: Mar 2020
Final results: Apr 2020
Clinical study report finalization: Apr 2020
Final report of the study result: Apr 2020</td></tr>
</table>

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned Date
Feasibility assessment	Jun 2019
Protocol finalization	Dec 2019
Statistical and epidemiological analysis plan	Mar 2020
Start of data collection	DD Month YYYY
End of data collection	DD Month YYYY
Statistical and epidemiological analysis report	Mar 2020
Final results	Apr 2020
Clinical study report	Apr 2020
Final report of study results:	Apr 2020

7. RATIONALE AND BACKGROUND

Stroke is the leading cause of mortality in China, resulting in about 1.9 million deaths in 2013[P20-03289]. Intravenous recombinant plasminogen activator (IV-rtPA) has been demonstrated to be essential to decrease disability among acute ischemic stroke (AIS) patients. However, currently a large number of stoke patients who have arrived hospitals on time and with no documented absolute contraindications for IV-rtPA are not receiving the thrombolysis treatment in China0 [P14-16838]. Since 2015, Chinese government and professional societies have put a lot of efforts in improving the quality of stroke care, including supporting hospitals to build stroke centers/units, encouraging stroke centers to submit thrombolysis treatment data, and issuing stroke care quality reports.

The China National Stroke Registry (CNSR), sponsored by the China Ministry of Health (MOH), is a nationwide hospital-based, prospective stroke registry for patients presented to hospitals with acute cerebrovascular events. The primary objectives of CNSR are to evaluate the quality of care during the acute hospitalization phase for cerebrovascular patients. The objectives are evaluated based on the performance indicators for stroke care delivery, and factors associated with the performance indicators are identified. The secondary objectives of CNSR include measuring longitudinal trends in clinical/functional outcomes of cerebrovascular patients at 3 months, 6 months, and 12 months after disease onset, the relationship between the clinical/functional outcomes of the patients with the quality of care during acute hospitalization, and adherence of the patients to secondary stroke prevention medication [P11-07866]. Patients had been continually enrolled for 8-12 months every five years since 2007. Data collected for each patient included demographics, medical history, initial, National Institutes of Health Stroke Scale (NIHSS) score, time intervals related to symptom onset, hospital arrival, and IV-rtPA treatment during the acute hospitalization phase.

Till 2017, three waves of CNSR were completed: 2007-2008 (CNSR I), 2012-2013 (CNSR II), and 2015-2017 (CNSR III). The number of hospitals participating each of CNSR were 132, 219, and 201, respectively. When compared to CNSR I, data from CNSR II showed a 1.17-fold increase in the adjusted odds of delivering evidence-based performance metrics for ischemic stroke (IS) care. Nevertheless, no statistically significant difference in the proportion of patient who received intravenous thrombolytics (IVT) treatment within 3 hours (h) of symptom onset was observed between the two CNSR [P20-03289].

In China, IV-rtPA was approved for the treatment of AIS patients within 3h of symptom onset without absolute contraindications. However, in 2008, the European Cooperative Acute Stroke Study (ECASS) III study concluded that AIS patients could still benefit from IV-rtPA treatment when given between 3h and 4.5 [P08-12177]the Chinese treatment guideline for AIS was updated in 2010, for which a recommendation of IV-rtPA treatment within 3h to 4.5h of symptom onset was added [P20-03291].

The current study aims at evaluating differences, if any, in clinical practice of IV-rtPA treatment among AIS patients from 2007 to 2017. In addition, the study will also provide information on the demographic and clinical characteristics of AIS patients receiving IV-rtPA in China. Taken together, the study will help us to better understand the trend of clinical practices for AIS treatment in China during the last decade, especially after the update of the

national AIS treatment guideline and the continuous efforts made by academic society and MOH in the field of stroke care.

8. RESEARCH QUESTION AND OBJECTIVES

The present study is to be conducted based on the AIS patient data collected from CNSR I, II, and III.
The primary objectives are:

- To investigate the temporal changes in the proportion of IV-rtPA treatment from 2007 to 2017 among IVT-eligible patients (patient groups B and B') and overall AIS patients (patient group A) in China;
- To investigate the temporal changes in IV-rtPA treatment time intervals from 2007 to 2017 among IV-rtPA-treated patients (patient groups C and C') in China.

The secondary objectives are:

- To describe the demographic and clinical characteristics of the IV-rtPA-treated patients (patient groups C and C'), IVT-eligible patients (patient groups B and B') and the overall AIS patients (patient group A) from 2007 to 2017 from the CNSR I to III.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a non-interventional study based on existing data. We will analyze data from three cross-sectional surveys of AIS patients in China: CNSR I (2007-2008), II (2012-2013), and III (2015-2017).

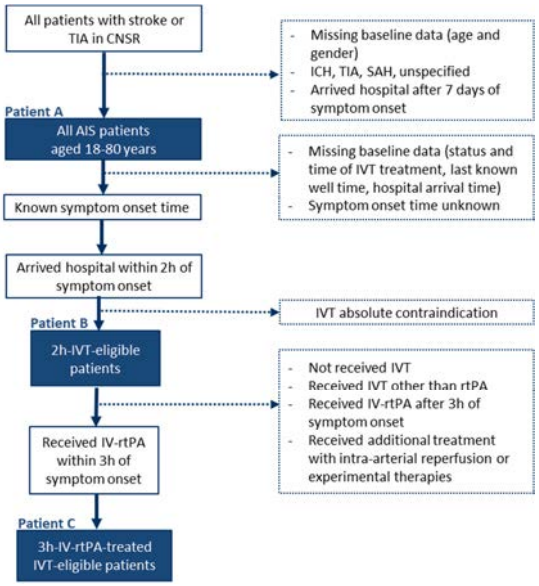
9.2 SETTING

In this study, AIS patient data from CNSR I to III will be used. The study will analyze data for the following patient groups:

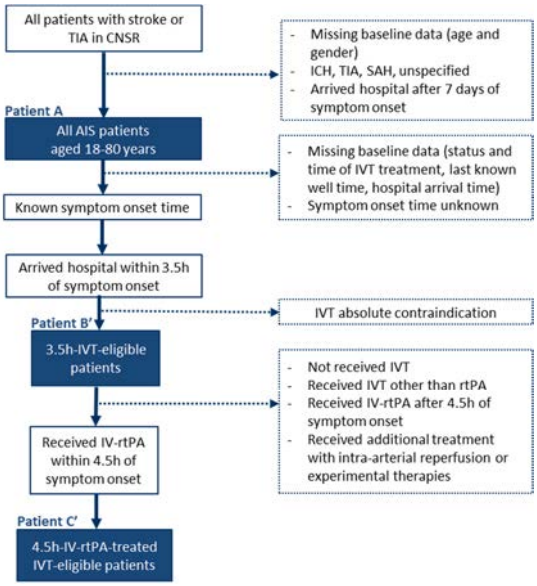
(1) All AIS patients (patient group A): the overall AIS patients aged 18-80 years who arrived at hospital within 7 days of symptom onset;
(2) IVT-eligible patients (patient groups B and B'): AIS patients who arrived at hospital within 2h (patient group B) and 3.5h (patient group B') of symptom onset and with no documented absolute contraindications to IVT treatment;
(3) IV-rtPA-treated patients (patient groups C and C'): IVT-eligible patients who arrived at hospital within 2h of symptom onset and received IV-rtPA within 3h of symptom onset (patient group C) and those who arrived at hospital within 3.5h of symptom onset and received IV-rtPA within 4.5h of symptom onset (patient group C').

The flow of data selection for each of the three reporting patient groups is depicted in Figure *1* below.

Figure 1 Patient groups selected for the time-trend study



(a) Patient groups A, B, and C



(b) Patient groups A, B', and C'

The in- and exclusion criteria for each of the reporting groups are listed below:

1) All AIS patients (patient group A)

1. Inclusion criteria:
   (1) Aged 18-80 years
   (2) Diagnosed with AIS on admission
2. Exclusion criteria:
   (1) Missing baseline data including age and gender
   (2) Diagnosed with intracranial hemorrhage (ICH), Transient Ischemic Attack (TIA), subarachnoid hemorrhage (SAH), or unspecific stroke
   (3) Arrived at hospital after 7 days of symptom onset

2) IVT-eligible patients (patient groups B and B')

1. Inclusion criteria:
   (1) Met the in- and exclusion criteria of "all AIS patients"
   (2) Arrived at hospital within 2h (patient group B) or 3.5h (patient group B') of symptom onset
2. Exclusion criteria:
   (1) Missing key data including
      i. symptom onset time (or last known well time);
      ii. hospital arrival time;
      iii. whether received IVT treatment or not;
      iv. the time of IVT treatment
   (2) Documented IVT absolute contraindications, according to the case report form (CRF) for each wave of CNSR (please refer to ANNEX 3 for details)

3) IV-rtPA-treated patients (patient groups C and C')

1. Inclusion criteria:
   (1) Met the in- and exclusion criteria of "IVT-eligible patients"
   (2) Treated with IV-rtPA within 3h (patient group C) or 4.5h (patient group C') of symptom onset
2. Exclusion criteria:
   (1) Not received IVT
   (2) Received IVT other than rtPA
   (3) Treated with IV-rtPA after 3h (patient group C) or 4.5h (patient group C') of symptom onset
   (4) Received additional treatments with intra-arterial reperfusion or experimental therapies

9.3 VARIABLES

9.3.1 Exposures

The study is descriptive in nature. It will not assess the association between any exposure and outcomes.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

For all the three waves of CNSR, the following primary outcomes will be assessed:

- Proportion of patients who received IV-rtPA treatment within 3h of symptom onset (patient group C, please refer to Figure *1* for details on patient groups) among 2h IVT-eligible patients (patient group B);
- Proportion of patients who received IV-rtPA treatment within 4.5h of symptom onset (patient group C') among 3.5h IVT-eligible patients (patient group B').

9.3.2.2 Secondary outcomes: the analysis will be performed for each wave of CNSR

Among all AIS patients (patient group A), the following secondary outcomes will be assessed:

- Proportion of patients who arrived at hospital within 2h of symptom onset and who received IV-rtPA treatment within 3h of symptom onset (patient group C);
- Proportion of patients who arrived at hospital within 3.5h of symptom onset and who received IV-rtPA treatment within 4.5h of symptom onset (patient group C');

Among 3h IV-rtPA-treated patients (patient group C), the following secondary outcomes will be assessed

- The door-to-needle (DTN) time (time between arrival at hospital and the administration of IV-rtPA treatment);
- Proportion of patients DTN time ≤ 60 minutes (min);
- Time between symptom onset and arrival at hospital;
- Time between symptom onset and the administration of IV-rtPA treatment.

Among 4.5h IV-rtPA-treated patients (patient group C'), the following secondary outcomes will be assessed

- The DTN time;
- Proportion of patients DTN time ≤ 60 min;
- Time between symptom onset and arrival at hospital;
- Time between symptom onset and the administration of IV-rtPA treatment.

[redacted]

9.4 DATA SOURCES

The current study will be conducted based on data collected from the three waves of CNSR.

CNSR I (2007-2008) used IS patient data from 132 hospitals in China, including 100 tertiary and 32 urban hospitals. Ischemic stroke patients aged 18 years and older within 14 days of symptom onset were included for the study. Paper-based registry forms (PRF) developed by the expert advisory panel were used for data collection. Patient information including demographics (age, gender, etc.), NIHSS, medical history (diabetes mellitus, hypertension, coronary heart disease/previous myocardial infarction, atrial fibrillation, previous stroke, TIA, dyslipidemia), symptom onset-to-door time, health insurance schemes (urban basic medical insurance schemes for urban and governmental employees and urban residents, new rural cooperative medical schemes for rural residents, commercial insurance, and self-payment [P20-03289]), vascular risk factors, imaging [mainly magnetic resonance imaging (MRI) or magnetic resonance angiography (MRA)], blood sampling, time-related variables [symptom onset time, hospital arrival time, CT time, IV-rtPA treatment time, etc.], implementation of performance measures for acute stroke care, final diagnosis, length of stay, in-hospital death, and follow-up information for 3-month, 6-month, and 12-month was collected. Hospital-level information including geographic region (e.g., east, central, or west, according to the annual report on health statistics of China [R20-1011])), teaching status, hospital bed size, and annual stoke volume was collected*0*.

CNSR II (2012-2013) used IS patient data from 219 hospitals in China. IS patients aged 18 years and older within 7 days of symptom onset were included for the study. Web-based case report forms (CRF) were used for data collection. Patient information including

demographics, NIHSS, medical history, symptom onset-to-door time, health insurance schemes, vascular risk factors, imaging, blood sampling, time-related variables, implementation of performance measures for acute stroke care, final diagnosis, length of stay, modified Rankin scale at discharge, and in-hospital death was collected. Follow-up information for 3-month, 6-month, and 12-month was collected by phone interview. Hospital-level information including geographic region, teaching status, hospital bed size, and annual stoke volume was collected [P20-03289].

CNSR III (2015-2017) used AIS or TIA patient data from 201 hospitals in China. AIS or TIA patients aged 18 years and older within 7 days of symptom onset were included for the study. An electronic data collection (EDC) system was used through an electronic software or the internet. Patient information including demographics, NIHSS, medical history, symptom onset-to-door time, health insurance schemes, vascular risk factors, imaging, blood sampling, time-related variables, implementation of performance measures for acute stroke care, final diagnosis, length of stay, modified Rankin scale at discharge, and in-hospital death was collected. Follow-up information for 3-month, 6-month, and 12-month was collected by phone interview. Hospital-level information including geographic region, teaching status, hospital bed size, and annual stoke volume was collected.

9.5 STUDY SIZE

It was estimated that in CNSR I, II, and III, the number of total AIS patients is 14704, 19604, and 15204, respectively.

Assuming the IV-rtPA-treated among IVT-eligible patients in CNSR I, II, and III are 4%, 5%, and 28% with the 95% confidence interval (CI) for each wave as below, then which can be distinguished with current study size.

CNSR	I	II	III
Assumed IV-rtPA proportion among eligible patients % (95% CI)	4% (3.7-4.3%)	5% (4.7-5.3%)	28% (27.3-28.7%)

No formal sample size calculation is performed due to the nature of this study. All eligible AIS patients within the existing database from the three waves of CNSR will be included in this study.

9.6 DATA MANAGEMENT

For the CNSR, all hospitals participating in the CNSR were selected by a Steering Committee using a convenient sampling method from the China National Network of Stroke Research developed by the National Center of Quality Management in Stroke Care. In total, 491 hospitals were included based on their geographic region, teaching status, hospital beds, and annual stroke discharges. The internal data validity of CNSR I, II, and III were ensured by introducing trained clinical research coordinators (CRCs) to these studies to guarantee the quality of data entry. The CRCs examined all medical records of stroke or TIA patients to identify eligible cases for the registries. The operating books were printed and sent to each

researcher and coordinator for guidance. Independent contract research organizations (CROs) were invited to monitor the study procedures and to ensure the quality of data entry. All data elements collected by PRF, web-based CRF, or EDC system were manually or mechanically checked for completeness, coding correctness, and appropriateness of the diagnostic algorithm conducted by a research specialist from independent CROs throughout the study period. A professional data processing company was responsible for the computer or PAD data entry. The Data Management Group of the National Clinical Research Center for Neurological Diseases (NCRC-ND) served as the data analysis department and analyzed the aggregated de-identified data for research purposes.

For the current study, the data will be managed by NCRC-ND. Data management, tabulations, and graphics will be carried out with SAS version 9.3 software (SAS institute). Source code of data management and data analyses will be kept for inspection for at least five years after publication of the results.

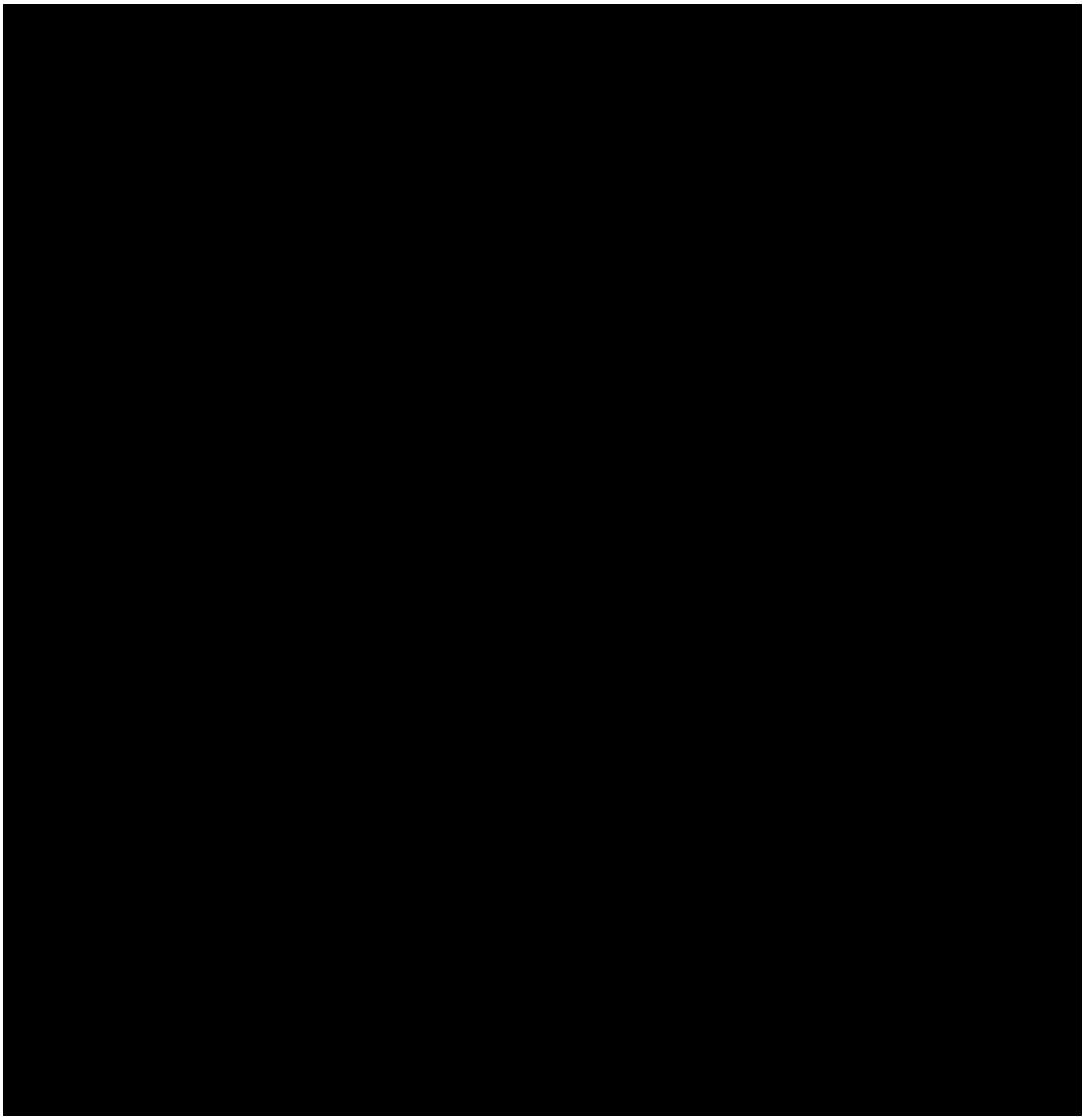
9.7 DATA ANALYSIS

9.7.1 Main analysis

For continuous data, descriptive statistics (number of patients, mean, standard deviation (SD), minimum, median, interquartile range, and maximum) will be presented. Categorical data will be presented as frequency and proportion with 95% CI. Unless otherwise stated, the calculation will be based on the available data. No data imputation will be performed for the missing data. Details for all analyses will be provided in the statistical analysis plan (SAP).

[redacted]

[redacted]



9.8 QUALITY CONTROL

For the CNSR, safety and risk control was assessed by the Data Safety and Monitoring Board (DSMB) before the study. Clinical research associates conducted data verification on site during the study. Data management team of NCRC-ND performed remote real time data supervision for all the data cleaning, integration, analysis, and other processing.

For the current study, the standard operation procedures (SOPs) of Boehringer Ingelheim (BI), such as NISed SOP, will be strictly followed. In addition, key elements of the International Society for Pharmacoepidemiology Good Pharmacoepidemiology Practices (GPP) will be followed [R16-5416]. The statistical analysis method will be reviewed and repeated by a second analyst. All the data cleaning, integration, analysis, and other processing will be conducted

under the guidance and supervision of data management team of NCRC-ND. The study report will be reviewed, approved, and archived per SOPs of BI.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The quality of a study based on existing data relies on accuracy of recorded data. Important data may not be available. The hospitals participating in the CNSR, although spread throughout China and covered all geographic areas, were mainly selected by convenience in nature. These hospitals possess more resources and expertise in ischemic stroke when compared to other hospitals in China, especially those at a country-level or lower ranks. Therefore, results from the current study will have to be interpreted with caution as it is not known what proportion of stroke patients in China have access to hospital cares at a level similar to those participated in the CNSR. Due to the nature of explore existing data, the interpretation is based on non-missing data.

9.10 OTHER ASPECTS

CNSR I, II, and III data collection were initiated after receiving approval from the central institutional review board at [redacted]. The informed consent forms (ICFs) were provided by patients or their legal representatives.

For the current study, the study protocol will be submitted to [redacted] Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for review. The IRB/IEC approval will be obtained before the study initiation. A waiver for the ICF will be applied since the study will use existing data.

9.11 SUBJECTS

9.11.1 Cases

Not applicable.

9.11.2 Controls

Not applicable.

9.12 BIAS

Refer to Section 9.9.

10. PROTECTION OF HUMAN SUBJECTS

The section is not applicable since the current study is a time-trend analysis of the data collected from the CNSR I to III.

The procedures set out in this study protocol are designed to ensure that the sponsor and investigator abide by the principles of the GPP guidelines [R16-5416]. The study also will be carried out in keeping with local legal requirements.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The current study is a time-trend analysis of the existing data collected from the CNSR I to III. Boehringer Ingelheim or third party acting on behalf of BI will not have access to individual patient data during the study. Data will be provided to BI in aggregated manner. Thus, collection and reporting of adverse events (AEs)/adverse drug reactions (ADRs) is not applicable.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The final report of the study report is planned in March 2020. Results of this non-interventional study will be disclosed on encepp.eu and clinicaltrials.gov.

A conference abstract and at least one manuscript will be generated from the study.

13. REFERENCES

13.1 PUBLISHED REFERENCES

[P08-12177] Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, von Kummer R, Wahlgren N, Toni D; ECASS investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke, N Engl J Med. 2008; 359(13):1317-1329.

[P11-07866] Wang Y, Cui L, Ji X, Dong Q, Zeng J, Wang Y, Zhou Y, Zhao X, Wang C, Liu L, Nguyen-Huynh MN, Claiborne Johnston S, Wong L, Li H; China national stroke registry investigators. The China national stroke registry for patients with acute cerebrovascular events: design, rationale, and baseline patient characteristics, Int J Stroke. 2011; 6(4):355-361.

[P14-16838] Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, Grotta J, Howard G, Kaste M, Koga M, von Kummer R, Lansberg M, Lindley RI, Murray G, Olivot JM, Parsons M, Tilley B, Toni D, Toyoda K, Wahlgren N, Wardlaw J, Whiteley W, del Zoppo GJ, Baigent C, Sandercock P, Hacke W; Stroke thrombolysis trialists' collaborative group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials, Lancet. 2014; 384(9958):1929-1935.

[P20-03289] Li Z, Wang C, Zhao X, Liu L, Wang C, Li H, Shen H, Liang L, Bettger J, Yang Q, Wang D, Wang A, Pan Y, Jiang Y, Yang X, Zhang C, Fonarow GC, Schwamm LH, Hu B, Peterson ED, Xian Y, Wang Y, Wang Y; China national stroke registries. Substantial progress yet significant opportunity for improvement in stroke care in China, Stroke. 2016; 47(11):2843-2849.

[P20-03291] Acute Ischemic Stroke Treatment Guideline Writing, Cerebrovascular Group, Neurology Sub association, Chinese Medical Association. Chinese Acute Ischemic Stroke Treatment Guideline 2010, Chin J Neurol. 2010; 43(2):146-153.

[R16-5416] International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP), Pharmacoepidemiol Drug Saf. 2015; 25(1): 2-10.

13.2 UNPUBLISHED REFERENCES

[R20-1011] 2013 China Health Statistical Yearbook
http://www.nhc.gov.cn/htmlfiles/zwgkzt/ptjnj/year2013/index2013.html

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: Temporal trends of thrombolysis treatment in Chinese acute ischemic stroke (AIS) patients from 2007-2017: analysis of China National Stroke Registry (CNSR) I, II, and III

EU PAS Register® number: Not applicable
Study reference number (if applicable):

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☐	☐	☐	
1.1.2 End of data collection[2]	☐	☐	☐	
1.1.3 Progress report(s)	☐	☐	☐	
1.1.4 Interim report(s)	☐	☐	☐	
1.1.5 Registration in the EU PAS Register®	☐	☐	☐	
1.1.6 Final report of study results.	☐	☐	☐	

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☐	☐	☐	
2.1.2 The objective(s) of the study?	☐	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☐	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☐	
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☐	

Comments:

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☐	☐	☐	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design	Yes	No	N/A	Section Number
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☐	☐	☐	
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☐	
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☐	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☐	

Comments:

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☐	☐	☐	
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☐	☐	☐	
4.2.2 Age and sex	☐	☐	☐	
4.2.3 Country of origin	☐	☐	☐	
4.2.4 Disease/indication	☐	☐	☐	
4.2.5 Duration of follow-up	☐	☐	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☐	☐	☐	

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☐	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☐	
5.3 Is exposure categorised according to time windows?	☐	☐	☐	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☐	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☐	

Comments:

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☐	☐	☐	
6.2 Does the protocol describe how the outcomes are defined and measured?	☐	☐	☐	
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☐	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☐	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☐	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☐	

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☐	

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☐	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☐	☐	
9.1.3 Covariates and other characteristics?	☐	☐	☐	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☐	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☐	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☐	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☐	
9.3.3 Covariates and other characteristics?	☐	☐	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☐	

Comments*:*

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☐	☐	☐	
10.2 Is study size and/or statistical precision estimated?	☐	☐	☐	
10.3 Are descriptive analyses included?	☐	☐	☐	
10.4 Are stratified analyses included?	☐	☐	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☐	
10.8 Are relevant sensitivity analyses described?	☐	☐	☐	

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☐	☐	
11.2 Are methods of quality assurance described?	☐	☐	☐	
11.3 Is there a system in place for independent review of study results?	☐	☐	☐	

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☐	
12.1.2 Information bias?	☐	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☐	

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☐	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☐	
13.3 Have data protection requirements been described?	☐	☐	☐	

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☐	☐	☐	

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☐	☐	☐	
15.2 Are plans described for disseminating study results externally, including publication?	☐	☐	☐	

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

A3-1 DIVISION OF EASTERN, CENTRAL, AND WESTERN CHINA [R20-1011]

The eastern region includes 11 provinces and municipalities in Beijing, Tianjin, Hebei, Liaoning, Shanghai, Jiangsu, Zhejiang, Fujian, Shandong, Guangdong, and Hainan; the central region includes 8 provinces in Shanxi, Jilin, Heilongjiang, Anhui, Jiangxi, Henan, Hubei, and Hunan; the western region includes 12 provinces, autonomous regions, and municipalities in inner Mongolia, Chongqing, Guangxi, Sichuan, Guizhou, Yunnan, Tibet, Shaanxi, Gansu, Qinghai, Ningxia, and Xinjiang.

A3-2 DOCUMENTED INTRAVENOUS THROMBOLYTICS ABSOLUTE CONTRAINDICATIONS

For CNSR I:

- Aged above 80 years;
- CT evidence of intracranial haemorrhage;
- CT evidence of early signs of large cerebral infarction;
- Concurrence of epileptic seizures during ischemic;
- Have suffered a stroke or severe head injury in the past 3 months;
- Uncontrolled hypertension despite active treatment. Uncontrolled hypertension refers to systolic blood pressure > 185 mmHg or diastolic blood pressure > 110 mmHg, measured at least 10 minutes apart and repeated 3 times;
- Known hemorrhagic condition with significant bleeding disorder at onset or within the past 6 months;
- Acute pancreatitis or proven ulcerative gastrointestinal disease within 3 months;
- Recent invasive cardiopulmonary resuscitation or childbirth within 10 days. Non-stress vascular puncture (such as subclavian vein or femoral vein puncture);
- Blood glucose < 50 mg/dl (2.7 mmol/l) or > 400 mg/dl (22.2 mmol/l);
- Platelet count < $10^5/mm^3$;
- Prothrombin time (PT) (international normalized ratio [INR]) > 1.5 or PT > 15 or activated partial thromboplastin time (APTT) > 40 sec.

For CNSRII and III:

- Uncontrolled hypertension despite active treatment. Uncontrolled hypertension refers to systolic blood pressure > 185 mmHg or diastolic blood pressure > 110 mmHg （;
- Concurrence of epileptic seizures during ischemic stroke;
- Recent surgery or trauma within 15 days;
- Recent intracranial or spinal surgery, head trauma, or stroke within 3 months;
- Previous history of intracranial haemorrhage, aneurysm, vascular malformation, or brain tumor;
- Active visceral bleeding within 22 days;

- Platelet count $<10^5/mm^3$, APTT (after heparin treatment) > 40 sec, PT > 15 or PT (INR) > 1.7, or known hemorrhagic condition/suspected subarachnoid hemorrhage
- CT evidence of ICH, SAH, or signs of large infarction.