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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Actilyse			
Name of active ingredient: alteplase			
Report date: **Special Disclosure Synopsis** <10 NOV 2021>	**Study number:** 0135-0343	**Version/Revision:** 1.0	**Version/Revision date:** NA
Title of study:	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		
Keywords:	Acute ischemic stroke; Thrombolysis; CNSR;		
Rationale and background:	The Chinese treatment guideline for AIS was updated in 2010 where the recommended time window for intravenous recombinant plasminogen activator (IV-rt-PA) treatment was extended from 3h since symptoms onset to 4.5h. Along with the development of stroke centers and stroke care quality control system, in order to understand the impact of these efforts on the clinical practices for AIS treatment in China, this study was initiated to evaluate the temporal changes from 2007 to 2017, in the IV-rt-PA treatment proportion and treatment time intervals of AIS patients.		
Research question and objectives:	Research question： Whether the quality of IV-rt-PA treatment thrombolysis treatment has been improved with the continuous development of stroke centers and stroke care quality control networks supported by academic society and MOH during the last decade in China? Primary Objectives: • To investigate the temporal changes in the proportion of IV-rt-PA treatment from 2007 to 2017 among intravenous thrombolytics (IVT) eligible patients and overall AIS patients in China; • To investigate the temporal changes in IV-rt-PA treatment time intervals from 2007 to 2017 among IV-rt-PA treated patients in China. Secondary Objectives: • To describe the demographic and clinical characteristics of the IV-rt-PA treated patients, IVT eligible patients and the overall AIS patients from the CNSR I to III.		
Study design:	This study was non-interventional and exploratory, while the 10-year time window was made possible by combining existing data from three cross-sectional surveys of AIS patients in China: CNSR I (2007-2008), II (2012-2013), and III (2015-2017).		

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Setting:	This study used AIS patient data from CNSR I to III, stretching across a 10-year time frame from 2007 to 2017. CNSR is a nationwide, prospective stroke registry where patients with acute cerebrovascular diseases were continuously enrolled for 8-12 month every 5-year since 2007.		
Subjects and study size, including dropouts:	The study included 42188 (Phase I: 10968; II: 17823; III: 13397) eligible patients from the CNSR I-III database who were aged 18-80 years diagnosed with AIS on admission and were admitted to hospital within 7 days of symptom onset. The inclusion and exclusion criteria and actual patient number of each reporting group are listed below:		

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	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 Patients in group A: CNSR I:10968; CNSR II 17823; CNSR III 13397. **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 Patients in group B: CNSR I:866; CNSR II 2214; CNSR III 1679. Patients in group B': CNSR I:1271; CNSR II 3684; CNSR III 2787. **3) IV-rt-PA-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-rt-PA 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 rt-PA (3) Treated with IV-rt-PA 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 Patients in group C: CNSR I:101; CNSR II 236; CNSR III 483. Patients in group C': CNSR I:172; CNSR II 262; CNSR III 932.
Variables and data sources:	Patient demographic and clinical characteristics of the IV rt-PA treated patients (patient groups C and C'), IVT eligible patients (patient groups B

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and B') and the overall AIS patients (patient group A) from the CNSR I to III were described.

Primary outcomes:

Proportion of patients who received IV rt-PA treatment within 3h of symptom onset (patient group C) among 2h IVT eligible patients (patient group B); Proportion of patients who received IV rt-PA treatment within 4.5h of symptom onset (patient group C') among 3.5h IVT eligible patients (patient group B'). Subgroup analysis by region and hospital level were also performed.

Secondary outcomes:

Among all AIS patients (patient group A), the following secondary outcomes were assessed: Proportion of patients who arrived at hospital within 2h of symptom onset and who received IV-rt-PA 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-rt-PA treatment within 4.5h of symptom onset (patient group C')

Among 3h IV-rt-PA patients (patient group C) and 4.5h of symptom onset (patient group C') for all three waves of CNSR:

- The door to needle (DTN) time (time between arrival at hospital and the administration of IV rt-PA treatment)
- Proportion of patients DTN time $\leqslant$ 60 minutes (min)
- Time between symptom onset and arrival at hospital
- Time between symptom onset and the administration of IV rt-PA treatment.

Further outcomes:

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

- Proportion of patients with a symptom onset-to-hospital arrival time within 2h, 3.5h, 4.5h, and 9h.

Among 2h IVT-eligible patients (patient group B), 3.5h IVT-eligible patients (patient group B'), 3h IV-rt-PA-treated patients (patient group C), and 4.5h IV-rt-PA-treated patients (patient group C') , the following outcome will be assessed :

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	• Proportion of patients who used Emergency Medical Service (EMS) from home to hospital for the three waves of CNSR.		
Results:	In CNSR I, II, and III, the proportion of patients treated with IV-rt-PA within 3 h among 2 h IVT-eligible patients was 11.66% (9.53%-13.80%), 10.66% (9.37%-11.94%), 28.77% (26.60%-30.93%), respectively. And the proportion of patients treated with IV-rt-PA within 4.5 h among 3.5 h IVT-eligible patients was 13.53% (11.65%-15.41%), 7.11% (6.28%-7.94%), and 33.44% (31.69%-35.19%), respectively. In CNSR I, II, and III, among all AIS patients (patient group A), proportion of patients who arrived at hospital within 2h of symptom onset and who received IV-rt-PA treatment within 3h of symptom onset (patient group C) was 0.92% (0.74%-1.10%), 1.32% (1.16%-1.49%), 3.61% (3.29%-3.92%), respectively. Proportion of patients who arrived at hospital within 3.5h of symptom onset and who received IV-rt-PA treatment within 4.5h of symptom onset (patient group C) was 1.57% (1.34%-1.80%), 1.47% (1.29%-1.65%), 6.96% (6.53%-7.39%). In CNSR I, II, and III, among 3h IV-rt-PA patients (patient group C), the median DTN time was 90 min (IQR 60-120), 100min (IQR 74-113), 58min (IQR 38-77); The proportion of patients with DTN time $\leqslant$ 60 min was 28.71% (19.89%-37.54%), 12.29% (8.1%-16.48%), 59.21% (54.83%-63.6%); The median OTD time was 60min (IQR 32.0–90.0), 59min (IQR 43.0–75.0), 69min (IQR 50.0–93.0); The median OTN time was 150min (IQR 138.0–170.0), 156min (IQR 141.0–165.0), 134min (IQR 108.0–155.0). In CNSR I, II, and III, among 4.5h IV-rt-PA patients (patient group C'), the median DTN time was 94 min (IQR 60-130), 95min (IQR 72-112), 60min (IQR38-84.5); The proportion of patients with DTN time $\leqslant$ 60 min was 26.74% (20.13%-33.36%), 13.36% (9.24%-17.48%), 53.43% (50.23%-56.64%); The median OTD time was 75min (IQR 42.5–110.0), 59min (IQR 45.0–84.0), 100min (IQR 60.0–140.0); The median OTN time was 175min (IQR 150.0–200.0), 159min (IQR 144.0–169.0), 170min (IQR 132.0–210.0). The mean and SD of age for CNSR I, II, and III groups were 63.5$\pm$11.1, 62.9$\pm$10.8, 61.2$\pm$10.4, and 62.5$\pm$10.8 for the total. 37%, 35.6% and 30.7% of the patients were female for CNSR I, II and III, respectively;		

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Discussion:	The results of this study showed that the proportion of patients who received IVT within 4.5 hours of symptom onset within the 3.5-hour IVT-eligible patients increased markedly in CNSR III versus CNSR I and II. This trend was similar for patients treated with IVT within 3 hours of symptom onset among the 2-hour IVT-eligible patients. The thrombolysis rates was observed to be lower for CNSR II and tier 2 hospitals subgroup. It was noted that CNSR II has a larger tier 2 hospital proportion, hence the difference in hospital distribution may have affected the overall thrombolysis rates.		
Marketing Authorisation Holder(s):	Boehringer Ingelheim (China) Investment Co., Ltd		
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