

Stroke Factors Associated with Thrombolysis Use in Hospitals in Singapore and US: A Cross-Registry Comparative Study

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Keywords

Stroke · Thrombolysis · Treatment · International comparison

Abstract

Background and Objectives: This paper aims to describe and compare the characteristics of 2 stroke populations in Singapore and in St. Louis, USA, and to document thrombolysis rates and contrast factors associated with its uptake in both populations. **Methods:** The stroke populations described were from the Singapore Stroke Registry (SSR) in Singapore and the Cognitive Rehabilitation Research Group Stroke Registry (CRRGSR) in St. Louis, MO, USA. The registries were compared in terms of demographics and stroke risk factor history. Logistic regression was used to determine factors associated with thrombolysis uptake. **Results:** A total of 39,323 and 8,106 episodes were recorded in SSR and CRRGSR, respectively, from 2005 to 2012. Compared to CRRGSR, patients in SSR were older, male, and from the ethnic majority. Thrombolysis rates in SSR and CRRGSR were 2.5 and 8.2%, respectively, for the study period. History of ischemic heart

disease or atrial fibrillation was associated with increased uptake in both populations, while history of stroke was associated with lower uptake. For SSR, younger age and males were associated with increased uptake, while having a history of smoking or diabetes was associated with decreased uptake. For CRRGSR, ethnic minority status was associated with decreased uptake. **Conclusions:** The comparison of stroke populations in Singapore and St Louis revealed distinct differences in clinicodemographics of the 2 groups. Thrombolysis uptake was driven by nonethnicity demographics in Singapore. Ethnicity was the only demographic driver of uptake in the CRRGSR population, highlighting the need to target ethnic minorities in increasing access to thrombolysis.

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Introduction

Thrombolysis via intravenous recombinant tissue plasminogen activator (rtPA) is a recommended treatment for ischemic strokes with optimal recovery rates

documented when administered within 3 h from stroke onset and moderate recovery for 3–4.5 h from onset [1]. Administration is traditionally carried out within stroke centers or hospitals with expertise and access to facilities such as cerebral angiography [2]. Thrombolysis rates reported in stroke registries vary widely across regions, from 0.6% in Taiwan [3] to 28% in Germany [4], due to different treatment type and time intervals from onset considered. Delivery of treatment has primarily been associated with health system factors, such as time to stroke discovery and expertise [5], but patient-level factors such as demographic characteristics and risk factors have also been influential on delivery of thrombolysis [6]. Hence, there is a need to understand thrombolysis use and its patient-level drivers, as well as its variation across different countries.

The global burden of stroke on populations worldwide is well established, causing the second highest disability adjusted life years in the world [7]. However, few studies focus on contrasting differences in stroke burden between Asian and Western stroke populations [8, 9]. A detailed comparison of individual-level stroke data from USA and Singapore will allow an examination of demographic and clinical characteristics of each population and facilitate better understanding of the clinical drivers and health challenges between the Asian and Western contexts. Therefore, the first aim of this paper was to describe and compare the stroke populations from hospitals in Singapore and USA, in terms of demographics, risk factor history, and thrombolysis rates. The second aim was to contrast the factors associated with use of thrombolytic therapy between the 2 registries. This study is the first to explore stroke in 2 multiethnic countries across Asian and Western contexts.

Methods

Two stroke registry datasets from Singapore and USA were combined and analyzed. Ethics approval for the analysis was obtained from the Institutional Review Board of the National University of Singapore and Washington University in St Louis. The methodology of data collection for both datasets has been described in detail elsewhere [10–12]. In brief, the dataset from Singapore consisted of deidentified stroke episodes from the Singapore Stroke Registry (SSR), accessed via the National Registry of Diseases Office (NRDO) under the Ministry of Health (MOH). The SSR received stroke case notifications from (1) all public healthcare institutions via the Hospital In-patient Discharge Summary, (2) MOH via information on medical claims to the government (MediClaims list), and (3) the national death registry. NRDO's Registry Coordinators verified the cases and ex-

tracted the detailed clinical information required by SSR, covering about 94% of strokes occurring in the country.

The stroke registry dataset from the USA consisted of stroke episodes from a prospective cohort of stroke patients served by the Comprehensive Stroke Center at the Barnes-Jewish Hospital (BJH) in St Louis, Missouri, collected by the Cognitive Rehabilitation Research Group (CRRG) at Washington University in St Louis. Consent for follow-up was given at point of interview during the hospital stay. Data were extracted from the hospital system for patients admitted between 1999 and 2017. Case notes were verified by registry coordinators and all patient information were exported into a standard report form. The deidentified CRRG data were combined with the SSR data in NRDO. Variables common to both registries were identified and reviewed to ensure the same definitions and categorizations were used. Thrombolysis was defined as the use of intravenous tPA in both registries.

Statistical Analysis

Only ischemic strokes that occurred between January 1, 2005, and December 31, 2012 (the overlapping period) in both registries were included in this study, using the definition of stroke by the World Health Organization with supporting radiological data and a set of International Classification of Diseases codes for ischemic stroke [10]. The 2 stroke populations were compared in terms of demographic factors and history of risk factors. The thrombolysis rates for the study period and by year were also assessed. Ethnicities in both populations were regrouped into majority and minority groups. For the SSR, patients of Chinese ethnicity were identified as the majority, while Malay, Indian, and other ethnicities were grouped together as the ethnic minority. For the CRRG Stroke Registry (CRRGSR), Caucasians were identified as the majority while African-American, Hispanic, Asian, and other ethnicities were grouped as the ethnic minority.

To examine the factors associated with thrombolysis, logistic regression was used with uptake as the outcome and models were built using pooled data from both countries, as well as for each country separately. Unadjusted logistic regression was used to identify factors independently associated with uptake, using a p value criterion of 0.05 and below for statistical significance. For multivariable analysis, all factors were included in the same model, and a backward stepwise approach was implemented for variable selection, using the abovementioned p value criterion to obtain a parsimonious model. ORs and their corresponding 95% CI were reported for each factor. Sensitivity analyses were carried out by building the same regression models using the respective ethnic groups of the 2 populations. All analyses were performed in RStudio [13].

Results

Clinicodemographic Profile of Both Stroke Populations

A total of 47,429 ischemic strokes were recorded from 2005 to 2012, with 39,323 and 8,106 episodes recorded in the SSR and CRRGSR, respectively (Table 1). The 2 stroke populations differed in most demographic characteristics, with a larger proportion of patients in the SSR being

Table 1. Characteristics of study populations from SSR (Singapore) and CRRGSR (St Louis, MO, USA)

	Combined (<i>n</i> = 47,429) <i>n</i> (%)	SSR (<i>n</i> = 39,323) <i>n</i> (%)	CRRGSR (<i>n</i> = 8,106) <i>n</i> (%)
Year of admission			
2005	5,332 (11.2)	4,662 (11.9)	670 (8.3)
2006	5,317 (11.2)	4,600 (11.7)	717 (8.8)
2007	5,641 (11.9)	4,801 (12.2)	840 (10.4)
2008	5,678 (12.0)	4,689 (11.9)	989 (12.2)
2009	5,979 (12.6)	4,887 (12.4)	1,092 (13.5)
2010	6,248 (13.2)	5,025 (12.8)	1,223 (15.1)
2011	6,591 (13.9)	5,219 (13.3)	1,372 (16.9)
2012	6,643 (14.0)	5,440 (13.8)	1,203 (14.8)
Age at stroke onset, years			
Median (IQR)	68.0 (58.0–78.0)	69.0 (59.0–78.0)	64.0 (53.0–76.0)
Range	15.0–115.0	15.0–115.0	18.0–90.0
Age group			
<50 years	4,829 (10.2)	3,382 (8.6%)	1,447 (17.9)
50–64 years	14,606 (30.8)	11,920 (30.3)	2,686 (33.1)
≥65 years	27,994 (59.0)	24,021 (61.1)	3,973 (49.0)
Gender			
Female	21,436 (45.2)	17,228 (43.8)	4,208 (51.9)
Male	25,993 (54.8)	22,095 (56.2)	3,898 (48.1)
Ethnic group			
Majority	34,043 (71.8)	29,519 (75.1)	4,524 (55.8)
Minority	13,386 (28.2)	9,804 (24.9)	3,582 (44.2)
Risk factors for stroke			
TIA	2,797 (5.9)	1,766 (4.5)	1,031 (12.7)
Stroke	12,665 (26.7)	10,237 (26.0)	2,428 (30.0)
Hypertension	36,206 (76.3)	29,868 (76.0)	6,338 (78.2)
Diabetes mellitus	17,781 (37.5)	15,876 (40.4)	1,905 (23.5)
Ischemic heart disease	12,092 (25.5)	9,612 (24.4)	2,480 (30.6)
Atrial fibrillation	5,808 (12.2)	4,636 (11.8)	1,172 (14.5)
Valvular heart disease	1,302 (2.7)	898 (2.3)	404 (5.0)
Peripheral heart disease	1,996 (4.2)	1,408 (3.6)	588 (7.3)
Smoking	18,421 (38.8)	15,169 (38.6)	3,252 (40.1)
Inpatient events			
CT/head scan	46,292 (97.6)	39,237 (99.8)	7,055 (87.0)
Thrombolysis	1,647 (3.5)	985 (2.5)	662 (8.2)
Length of stay, days			
Median (IQR)	5.0 (3.0–10.0)	6.0 (3.0–11.0)	3.0 (2.0–7.0)
Maximum	400.0	388.0	400.0
Discharge destination			
Deceased	3,317 (7.0)	2,957 (7.5)	360 (4.4)
Home (no rehabilitation)	17,812 (37.6)	15,915 (40.5)	1,897 (23.4)
Home (with rehabilitation)	8,039 (16.9)	5,915 (15.0)	2,124 (26.2)
Nursing home	2,534 (5.3)	1,655 (4.2)	879 (10.8)
Other hospitals	3,071 (6.5)	2,891 (7.4)	180 (2.2)
Inpatient rehabilitation hospital	12,656 (26.7)	9,990 (25.4)	2,666 (32.9)

TIA, transient ischemic attack; SSR, Singapore Stroke Registry; CRRGSR, Cognitive Rehabilitation Research Group Stroke Registry; IQR, interquartile range.

above 65 years old and belonging to the male sex or ethnic majority. The distributions of risk factors for stroke differed significantly between the 2 populations, with patients in the CRRGSR exhibiting a higher prevalence across all investigated factors, except for diabetes mellitus

(SSR 40.4%; CRRGSR 23.5%). For thrombolysis rates, 2.5% of episodes in the SSR were treated with thrombolysis, a lower rate in comparison to 8.2% in the CRRGSR (Table 1). Examining the rates by year, uptake increased over the study period in both countries (Fig. 1).

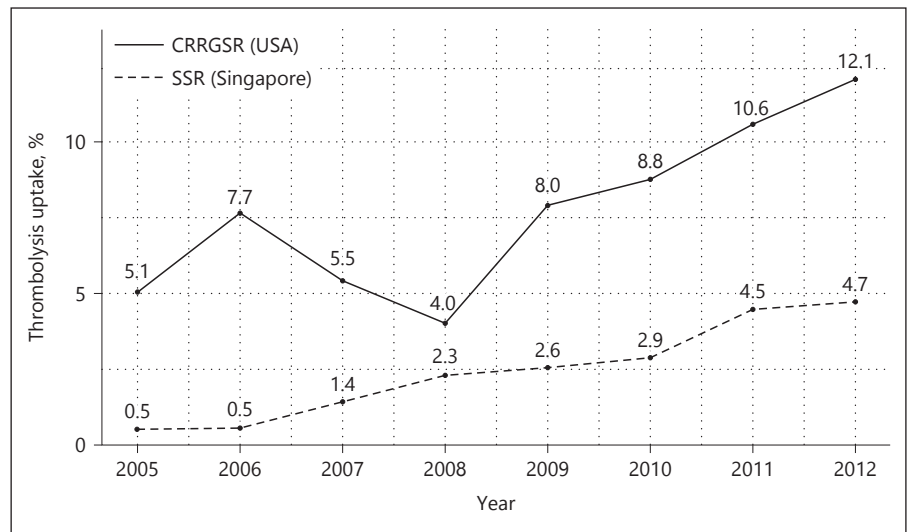


Fig. 1. Thrombolysis rates over time in CRRGSR and SSR. SSR, Singapore Stroke Registry; CRRGSR, Cognitive Rehabilitation Research Group Stroke Registry.

Factors Associated with Thrombolysis Uptake

From bivariable analysis of pooled information from both stroke populations (Table 2), being of older age was associated with lower thrombolysis uptake (OR 0.99, 95% CI 0.99–0.99), while male sex (1.17, 1.06–1.29) and ethnic minority (1.16, 1.04–1.29) were associated with higher thrombolysis uptake. Clinical risk factors such as having a history of transient ischemic attack (TIA; 1.28, 1.06–1.54), ischemic heart disease (1.30, 1.17–1.45), or atrial fibrillation (1.71, 1.51–1.94) were also associated with higher uptake. In contrast, history of stroke (0.58, 0.51–0.66) or diabetes (0.67, 0.60–0.74) was associated with lower rates of thrombolysis. In addition, uptake was significantly higher in all years after 2005, with the highest in 2012 (5.99, 4.53–7.93). In the multivariable analysis, younger age (0.99, 0.99–1.00), males (1.20, 1.08–1.33), history of ischemic heart disease (1.29, 1.15–1.46), and atrial fibrillation (1.74, 1.51–1.99) remained associated with thrombolysis use upon admission, while history of stroke (0.53, 0.47–0.61) or diabetes (0.81, 0.72–0.90) was associated with lower uptake.

Examining only the SSR population (Table 3), similar bivariable associations with thrombolysis uptake were observed, except for ethnicity (1.12, 0.97–1.29) and history of TIA (1.24, 0.94–1.64), which were no longer statistically significant. In the multivariable analysis, smoking was additionally found to be associated with lower uptake (0.78, 0.67–0.90). Sensitivity analyses did not show any statistically significant association of the different ethnic minorities with thrombolysis uptake (online suppl. Table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000502278). The uptake in-

creased significantly from 2007 onwards (2007: 2.78, 1.73–4.47; 2012: 9.35, 6.09–14.36).

For the CRRGSR population, bivariable associations were found similar to that in the pooled analysis, except for sex (1.13, 0.96–1.33) and history of diabetes (1.03, 0.86–1.24), which were no longer statistically significant (Table 3). In multivariable analysis, history of ischemic heart disease (1.22, 1.03–1.45) and atrial fibrillation (1.45, 1.18–1.79) were found to be associated with greater uptake of thrombolysis, while ethnic minority status (0.83, 0.70–0.98) and history of stroke (0.66, 0.54–0.80) were associated with lower uptake. Uptake increased significantly only from 2009 onwards (2009: 1.65, 1.09–2.48; 2012: 2.59, 1.76–3.81). Sensitivity analyses revealed the African-American minority, constituting 42.7% of the population, to be driving the association of the ethnic minority with lower thrombolysis uptake (online suppl. Table S1).

Discussion/Conclusion

The comparison of stroke populations from hospitals in Singapore and St Louis revealed distinct differences in clinicodemographics of the 2 groups. Findings revealed differing age distributions between the 2 registries, with younger patients in the CRRGSR than in the SSR. Hypertension, smoking, ischemic heart disease, diabetes, and prior stroke remain the top risk factors for both populations. This similarity in risk factor profile across these Western and Asian populations is consistent with the findings from comparative studies [8, 9], including the Global Burden of Disease Study 2013 [14]. With diabetes

Table 2. Logistic regression analyses of thrombolysis rates, using pooled data

	Bivariable OR (95% CI)	Multivariable OR (95% CI)
Country		
SG	1.00	1.00
USA	3.46 (3.13–3.83)***	3.10 (2.79–3.45)***
Demographics		
Age at admission	0.99 (0.99–0.99)***	0.99 (0.99–1.00)***
Gender		
Male	1.17 (1.06–1.29)**	1.20 (1.08–1.33)***
Ethnicity		
Minority	1.16 (1.04–1.29)**	
Admission year		
2005	1.00***	1.00***
2006	1.40 (0.99–1.97)	1.36 (0.97–1.92)
2007	1.91 (1.39–2.63)	1.80 (1.30–2.48)
2008	2.48 (1.82–3.37)	2.26 (1.66–3.08)
2009	3.40 (2.53–4.57)	3.06 (2.28–4.12)
2010	3.91 (2.92–5.22)	3.42 (2.56–4.58)
2011	5.66 (4.28–7.50)	4.87 (3.67–6.46)
2012	5.99 (4.53–7.93)	5.40 (4.07–7.15)
Risk factors		
TIA	1.28 (1.06–1.54)*	
Previous stroke	0.58 (0.51–0.66)***	0.53 (0.47–0.61)***
Hypertension	0.94 (0.84–1.05)	
Diabetes mellitus	0.67 (0.60–0.74)***	0.81 (0.72–0.90)***
Ischemic heart disease	1.30 (1.17–1.45)***	1.29 (1.15–1.46)***
Atrial fibrillation	1.71 (1.51–1.94)***	1.74 (1.51–1.99)***
Valvular heart disease	1.26 (0.96–1.65)	
Peripheral heart disease	1.17 (0.93–1.47)	
Smoking	0.99 (0.90–1.10)	

* $p < 0.05$.** $p < 0.01$.*** $p < 0.001$.

TIA, transient ischemic attack.

within the top 10 attributable risk factors for stroke in the high-income Asia-Pacific region [14], the implications of an increasing diabetes prevalence would include an increase in stroke burden in later years, motivating the need to ensure that the burden of diabetes in Singapore is addressed to tackle the future stroke burden in the country.

The increase in thrombolysis rates over time suggests increased awareness and advocacy of thrombolysis as an established stroke treatment [15]. The higher thrombolysis rates in the CRRGSR demonstrate the importance of system-level programs to increase quality of care and can be attributed to a decade long nationwide effort to improve hospital processes [16]. The Get With The Guidelines campaign by the American Stroke Association in the USA requires enrolled hospitals to achieve certain standards of care, such as meeting targeted rates of brain scans and

thrombolysis of patients. The association also recognizes hospitals that achieve excellence in these areas, encouraging greater adherence to clinical guidelines and subsequently increasing thrombolysis rates. In Singapore, the publication of the first set of Clinical Practice Guidelines (CPG) for stroke and TIAs in 2008 by the MOH could have contributed to the steady increase in thrombolysis rates in ensuing years. The CPG recommended the use of tPA for thrombolysis within 3 h of stroke onset [17]. This recommendation was revised in 2013 (after the period of study), in accordance with newer clinical evidence which demonstrated benefit to patients treated with tPA during the 3–4.5 h window period [18]. In addition to the use of the CPG, implementation of a guideline similar to Get With The Guidelines in Singapore could potentially encourage a further system-level increase in thrombolysis rates.

Table 3. Logistic regression analyses of thrombolysis rates, using country-specific data

	SSR (<i>n</i> = 39,323)		CRRGSR (<i>n</i> = 8,106)	
	bivariable OR (95% CI)	multivariable OR (95% CI)	bivariable OR (95% CI)	multivariable OR (95% CI)
Demographics				
Age at admission	0.98 (0.98–0.99)***	0.98 (0.98–0.99)***	1.01 (1.00–1.01)**	
Gender				
Male	1.37 (1.20–1.56)***	1.38 (1.18–1.60)***	1.13 (0.96–1.33)	
Ethnicity				
Minority	1.12 (0.97–1.29)		0.73 (0.62–0.86)***	0.83 (0.70–0.98)*
Admission year				
2005	1.00***	1.00***	1.00***	1.00***
2006	1.06 (0.60–1.88)	1.04 (0.58–1.84)	1.55 (1.00–2.42)	1.55 (1.00–2.42)
2007	2.90 (1.80–4.66)	2.78 (1.73–4.47)	1.08 (0.69–1.71)	1.07 (0.68–1.69)
2008	4.76 (3.03–7.47)	4.56 (2.90–7.17)	0.79 (0.49–1.26)	0.80 (0.50–1.28)
2009	5.29 (3.39–8.27)	4.98 (3.19–7.79)	1.62 (1.08–2.44)	1.65 (1.09–2.48)
2010	5.99 (3.85–9.32)	5.62 (3.61–8.75)	1.81 (1.22–2.70)	1.82 (1.22–2.71)
2011	9.47 (6.16–14.56)	8.85 (5.75–13.61)	2.23 (1.52–3.27)	2.23 (1.51–3.28)
2012	10.04 (6.54–15.41)	9.35 (6.09–14.36)	2.58 (1.76–3.80)	2.59 (1.76–3.81)
Risk factors				
TIA	1.24 (0.94–1.64)		0.76 (0.58–0.98)*	
Previous stroke	0.46 (0.39–0.55)***	0.48 (0.40–0.58)***	0.66 (0.55–0.80)***	0.66 (0.54–0.80)***
Hypertension	0.89 (0.77–1.03)		0.94 (0.78–1.14)	
Diabetes mellitus	0.69 (0.60–0.79)***	0.72 (0.63–0.83)***	1.03 (0.86–1.24)	
Ischemic heart disease	1.20 (1.04–1.38)*	1.41 (1.21–1.65)***	1.23 (1.04–1.45)*	1.22 (1.03–1.45)*
Atrial fibrillation	1.70 (1.44–2.00)***	1.89 (1.58–2.26)***	1.53 (1.25–1.88)***	1.45 (1.18–1.79)***
Valvular heart disease	1.16 (0.78–1.73)		0.90 (0.61–1.31)	
Peripheral heart disease	0.93 (0.66–1.32)		0.98 (0.72–1.33)	
Smoking	0.99 (0.87–1.12)	0.78 (0.67–0.90)***	0.96 (0.81–1.12)	

* *p* < 0.05.** *p* < 0.01.*** *p* < 0.001.

SSR, Singapore Stroke Registry; CRRGSR, Cognitive Rehabilitation Research Group Stroke Registry; TIA, transient ischemic attack.

The results of the multivariable analysis suggest differing barriers to stroke thrombolysis in both countries. Uptake of treatment appears to be dependent on age, sex, and risk factors of stroke patients in Singapore. We found females and smokers were associated with lower thrombolysis uptake in the SSR, which are in agreement with previous studies [19, 20]. The lower thrombolysis rates observed in females could potentially be attributed to delay in arrival time or higher stroke severity, which would preclude them from treatment [20, 21]. The lower treatment rates in smokers may be attributed to higher stroke severity and subsequently treatment ineligibility for smokers with small-vessel occlusions [22]. However, we were unable to perform a subgroup analysis to confirm this as ischemic stroke subtype information was not collected in this study. In the United States, ethnicity in contrast appears to be a dominant factor in the delivery of stroke treatment to a patient. The evident ethnic disparity in thrombolysis

rates in the CRRGSR is supported by the wealth of literature indicating racial-ethnic disparities in stroke care between white and minority communities [23–26]. Our results support the discussion advocating greater measures to narrow the gap in care for the minorities in the country and to address the underlying drivers of this disparity [23].

This study has several strengths. This study examined 2 multiethnic stroke populations using individual-level data, revealing associations of various factors with thrombolysis uptake. The completeness of coverage by the respective registries, as well as the use of retrospective data from hospital records of all stroke admissions, minimized selection, and recall bias. Any bias was also likely to be nondifferential across the patients who received and did not receive thrombolysis. This was because the registries were set up with collecting routine stroke data as a primary purpose, and information collected would not be associated with the outcome of thrombolysis or any spe-

cific characteristics of the patients. Attrition bias was minimal as all data were collected for a single admission, without the need for follow-up. As a nationwide stroke registry, the SSR would have reached all hospitalizations related to stroke in public hospitals, covering around 94% of all stroke cases in Singapore. Information collected is routine and standardized from the different hospitals, ensuring quality of the data. The CRRGSR was also comprehensive in coverage as it covered all patients in the region of St. Louis, Missouri, who sought care for stroke at BJH, which is the largest hospital in the state.

Limitations of this study include the inability to capture the data of stroke patients who sought help at the private hospitals in Singapore or other hospitals in St Louis. The results obtained may not also be generalizable to other stroke populations in the rest of the United States due to variations in demographic makeup. Consequently, the findings of this study cannot be generalized to reflect any nation-level differences in characteristics or trends. Furthermore, BJH as a regional stroke center receives stroke patients from neighboring sites who may have already received thrombolysis before transferring to BJH. The treatment rates reported in this paper would then reflect the thrombolysis usage in the hospital itself and would be a underestimate of the rate in the state. In addition, the uptake of thrombolysis was modeled in this paper to be dependent on patient-centric factors and did not account for the impact of health system factors affecting the administration of thrombolysis [5, 6]. In particular, history of medication use and door- or onset-to-needle time were not included as they were not available for the study period in both datasets. Also, stroke severity, measured by indices such as the National Institutes of Health (NIH) Stroke Scale [27], was similarly not available in the SSR for the study period as it was not routinely collected in hospitals in Singapore, limiting any conclusions to be made for the association between the stroke severity and thrombolysis uptake. The findings could also be affected by differences in treatment indications between the 2 populations, such as indications for patients aged 80 and above within 4.5 h of stroke onset by the American Stroke Association but not by the CPG. The lack of such information related to the eligibility of stroke patients arriving at the hospital could also potentially pose as confounders in identifying factors associated with thrombolysis uptake and should be obtained to refine the analysis in future work.

The detailed comparison of stroke registry data from Singapore and St Louis suggests that the characteristics of stroke patients in the 2 populations generally differ. Rates of thrombolysis were lower in Singapore than in the CRRGSR. Factors influencing the administration of thrombolysis

upon admission were similar in clinical risk factors across the 2 registries, but differed in demographic aspects, with age- and sex-driving uptake in Singapore, and ethnicity in the CRRG stroke population. However, both trends in uptake appear to be on the rise, suggesting that the increasing awareness and advocacy of thrombolysis may be translating to greater use over the period of 2005–2012.

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Statement of Ethics

The Washington University in St Louis Institutional Review Board and National University of Singapore Institutional Review Board approved a waiver of written consent for this study.

Disclosure Statement

The authors declare no conflicts of interest.

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Author Contributions

G.C.-H.K. and M.C.B.: conceptualized the study. A.W.K.W., C.H.C., and N.V.: facilitated the access and acquisition of the registry data. S.H.-X.N.: conducted the data analysis and drafted the manuscript with C.S.T., F.M.R., A.W.K.W., C.H.C., B.P.L.C., J.-M.L., and N.V.: provided critical revisions to the manuscript. All authors approved the final version of the manuscript.

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