ARTICLE

Incidence and functional outcome of atrial fibrillation and non-atrial fibrillation- related cardioembolic stroke in Joinville, Brazil: a population-based study

Incidência e desfecho funcional de AVC cardioembólico com e sem fibrilação atrial em Joinville, Brazil: estudo de base populacional

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ABSTRACT

Among ischemic strokes, cardioembolic (CE) stroke has the worst outcome. We measured the incidence of atrial fibrillation (AF) and non-AF related CE strokes, previous anticoagulant use, and the 90-day functional outcome. Using multiple overlapping sources, we included all CE strokes that occurred in 2015 in Joinville, Brazil. Of the 374 ischemic strokes, 23% (84) were CE. The CE age-adjusted incidence, per 1,000 person-years, was 0.14 (0.11–0.17). Of the 26 patients with known prior AF, 73% (19) were not anticoagulated, 77% (20) had a CHA_2DS_2VASc score ≥ 3 and 81% (21) had a HAS-BLED score < 3. After three months, approximately one third of those 26 patients died or became disabled. The incidence of CE stroke in our sample was lower than in other population-based studies. The opportunity for anticoagulation was missed in one third of cases.

Keywords: stroke; incidence; prognosis; population studies in public health.

RESUMO

Entre todos os subtipos de AVC isquêmico, os eventos cardioembólicos (CE) apresentam os piores prognósticos. Determinamos a incidência de AVC isquêmico CE, associada ou não à fibrilação atrial (FA), o uso prévio de anticoagulantes e os desfechos funcionais em Joinville, Brasil. Utilizando múltiplas e sobrepostas fontes de informação, registramos todos os primeiros eventos CE ocorridos em 2015. Entre 374 eventos isquêmicos, 23% (84) foram CE. A incidência ajustada, para qualquer fonte cardioembólica, foi 0.14 (0.11–0.17) por 1000 pessoas-ano. Entre 26 pacientes com FA previamente conhecida, 73% (19) não estavam anticoagulados, 77% (20) tinham ≥ 3 pontos na escala CHA_2DS_2VASc e 81 % (21) < 3 pontos na escala HAS-BLED. Após 3 meses, um terço destes 26 pacientes morreram ou ficaram dependentes. A incidência de AVC I CE em Joinville é menor do que em outros estudos de base populacional. Um terço dos casos de AVC I CE com FA previamente conhecida perderam a oportunidade de anticoagulação.

Palavras-chave: acidente cerebral vascular; incidência; prognóstico; estudos populacionais em saúde pública.

Worldwide, ischemic stroke is the most common major pathological type of stroke[1]. Among all ischemic stroke subtypes, cardioembolic (CE) stroke is particularly worrisome for two main reasons. The first one is demographic: as age is a risk factor for both atrial fibrillation (AF) and stroke, the aging of the population will progressively increase the burden of CE stroke in many countries.[1,2] The second reason involves outcomes: in a population-based study in Oxfordshire, UK, 2,555 ischemic stroke subtypes were followed up from 2002 to 2014. After six months, two thirds were dependent. After one year, 42% had died. These outcomes are significantly higher than those reported for other ischemic stroke subtypes[2].

Therefore, knowing the incidence of CE stroke is crucial for primary and secondary prevention policies[1,2,3].

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Conflict of interest: There is no conflict of interest to declare.

Received 16 June 2016; Received in final form 17 December 2016; Accepted 03 February 2017.

The age-adjusted incidence of CE stroke ranges from 17 to 40 per 100,000 person-years[4,5]. As the prevalence of AF increases, due partly to the aging population[6], we would expect more AF-related CE strokes in the future[7].

The Global Burden of Diseases Study Group showed that, from 1990 to 2013, 75% of deaths from strokes and 81% of the stroke-related disability-adjusted life years lost occur in low- and middle-income countries[8], where the progressive economic pressure of the growing elderly population is occurring[9]. However, little epidemiological data on CE stroke are available from those countries. To address this knowledge gap, we aimed to measure the incidence of AF-related and non-AF-related CE stroke, the stroke risk stratification scale distribution (CHA_2DS_2VASc) and 90-day modified Rankin scale proportions in Joinville, Brazil.

METHODS

The Joinville population registry

Joinville is a city in southern Brazil of 1,130 km^2 and with 516,288 inhabitants, according to the last national census in 2010[10]. The city has four hospitals (one with a stroke unit) and one public institutional care facility. The Joinville Stroke Registry is an ongoing population-based stroke data bank, which started in 2005, and has been supported by law since 2013[11]. The methods for stroke ascertainment in our registry have previously been published[12]. In brief, we used multiple overlapping sources of ascertainment according to the World Health Organization STEPS criteria[13].

Cohort sample

Over one year (April 2014 to March 2015), we included all patients with a first-ever ischemic stroke. We also included residents in the city with a confirmed stroke that occurred outside of the city limits. Patients with transient ischemic attacks were not included. We excluded stroke cases in which the patient died within the first 24 hours of symptom onset without a brain CT and no reliable medical record, as well as patients residing outside of the Joinville city limits.

Routine data collection

We obtained demographic, cardiovascular risk factor, biochemical, electrocardiographic (ECG) and radiological tests. All patients underwent at least one brain CT and transthoracic echocardiogram. Stroke diagnosis followed established diagnostic criteria[1,12,14]. The pathophysiological diagnosis of stroke was based on the criteria described in the Trial of ORG 10127 in the Acute Stroke Treatment (TOAST) study[15]. The stroke investigation routine followed the guidelines of the Brazilian Society of Cerebrovascular Diseases[16]. The Brazilian Economic Classification Criterion was the instrument chosen to evaluate the patients' economic class[17]. To calculate stroke risk in patients with AF, we used the CHA_2DS_2VASc

score[18]. To calculate the risk of bleeding on anticoagulation, we used the HAS-BLED score[19].

Cardioembolic diagnostic work-up

Holter monitoring was ordered in patients whose medical histories and physical examinations suggested a cardiac source of embolism and in patients with a cryptogenic diagnostic work-up. The ECGs with AF were classified as chronic, new or paroxystic. Chronic AF (known previously) included cases of long-standing AF confirmed by ECG (e.g., greater than one year), in which cardioversion was not indicated or attempted, usually leading to permanent AF[20]. When a patient had two or more episodes, AF was considered recurrent. When it spontaneously returned to sinus rhythm, AF was designated paroxysmal, and when it was sustained, AF was designated as new. In the latter case, termination by pharmacological therapy or electrical cardioversion did not change the designation[20]. In the hospitals, we asked about previous anticoagulant use and checked the intensity of anticoagulation against the International Normalized Ratio (INR) value. We registered the type of anticoagulant prescription at hospital discharge.

Evaluation of outcomes

Functional independence was evaluated using the modified Rankin scale (mRS), which ranges from 0 (no symptoms) to 6 (death)[21]. The mRS scores were assessed at one month (face-to-face) and at 90 days (by telephone) by interviewers who were blinded to the patient groups.

Statistical analysis

To calculate incidences and 95% confidence intervals (CI), we used the Poisson distribution for the number of events. We calculated the crude incidence rates for 2014-2015 as (total event cases)/(total population at risk). The population-at-risk data were extracted from the national census and from the last intercensal data[10]. Incidence was adjusted for age by the direct method using both the 2010 census population of Brazil and the SEGI "world" population as standards[22]. This study was approved by the Ethics in Research Committees.

RESULTS

From April 2014 to March 2015, we registered 429 patients with any type of first-ever stroke in Joinville. Of those, 87.2% (374/429) were ischemic strokes, 7.5% (32/429) were haemorrhagic stroke and 5.4% (23/429) were subarachnoid haemorrhage. Among the ischemic strokes, 26.5% (99/374) were small-vessel disease, 23.3% (87/374) were large-vessel disease, 22.5% (84/374) were CE, 15.2% (57/374) were undetermined and 12.6% (47/374) were other determined subtypes. The proportion of any type of AF among all ischemic stroke events was 11.4% (49/429), and 58.3% (49/84) of all CE strokes were AF-related.

Table 1 compares the demographic and clinical risk factor findings between 49 patients with AF-related and 35 patients with non-AF-related CE stroke. We found that patients with AF-related events were older than patients with non-AF (p < 0.001), had a slightly higher prevalence of hypertension (p = 0.05) and a lower prevalence of smoking habits (p < 0.01). As expected, the median on the HAS-BLED scale was higher in AF-related events (p = 0.01). Of the 26 patients who arrived in emergency departments with known prior AF, seven were using anticoagulants (four on warfarin, two on rivaroxaban, and one on dabigatran). Among those, 20 (76.9%) had a CHA_2DS_2VASc score ≥ 3, and 21 (80.8%) had a HAS-BLED score < 3. Of the four patients who were using warfarin, three had INR levels below the target, and the level was not determined for the last one.

Data are number of patients (%) unless otherwise indicated. Social class per Brazilian Criteria of Economic Classification based on 2013 National Household Sample Survey. Amounts per year in US dollars. Class: A = 64,020; B1 = 27,468; B2 = 19,980; C1 = 8,256; C2 = 4,572; D-E: 2,016. The Brazilian gross domestic product per capita at purchasing power parity per the World Bank in 2013 was US$14,997 per year in 2013. AF: atrial fibrillation; MI: myocardial infarction; CHF: chronic heart failure; BMI: body mass index; SD: standard deviation; NIHSS: National Institute of Health stroke scale.

The crude and age-adjusted incidences per 1,000 person-years of first-ever AF-related and non-AF-related events are shown in Table 2. The incidence per 1,000 patient-years, age-adjusted to the world population, was 0.10 (95% CI, 0.07–0.13)

Table 1. Demographic, socio-economic and cardiovascular risk factors of patients with AF and non-AF-related cardioembolic ischemic stroke.

Variable	AF (n = 49)	Non-AF (n = 35)	All CE (n = 84)	p-value
Demographic				
Men (SD)	19 (37.0)	19 (54.3)	38 (45.2)	18
Mean age (SD)	77.0 (10.5)	62.0 (14.4)	71.0 (14.2)	< 0.001
Education (years)				
Illiterate or <3 years	20 (40.8)	9 (25.7)	29 (34.5)	0.84
4 years	21 (42.9)	8 (22.9)	29 (34.5)	
8 years	4 (8.2)	6 (17.1)	10 (11.9)	
11 years	2 (4.1)	8 (22.9)	10 (11.9)	
> 11 years	1 (2.0)	3 (8.6)	4 (4.8)	
Social class*				
A1	0 (0.0)	0 (0.0)	0 (0.0)	1.0
A2	0 (0.0)	2 (5.7)	2 (2.4)	
B1	1 (2.0)	2 (5.7)	3 (3.6)	
B2	8 (16.2)	10 (28.6)	18 (21.4)	
C1	23 (46.9)	11 (31.4)	34 (40.5)	
C2	10 (20.4)	7 (20.0)	17 (20.2)	
D	5 (10.2)	3 (8.6)	8 (9.5)	
E	1 (2.0)	0 (0.0)	1 (1.2)	
Cardiovascular risk factors				
Hypertension	39 (79.6)	21 (60.0)	60 (714)	0.05
Diabetes mellitus	19 (38.8)	12 (34.3)	31 (36.9)	0.67
Dyslipidaemia	32 (65.3)	23 (65.7)	55 (65.5)	0.96
Current smoker	3 (6.1)	9 (25.7)	12 (14.3)	0.01
Ex-smoker	14 (28.6)	12 (34.3)	26 (31.0)	0.57
Never smoked	32 (65.3)	14 (40.0)	46 (54.8)	0.02
MI	0 (0.0)	2 (5.7)	2 (2.4)	0.17
CHF	14 (28.6)	17 (48.6)	31 (36.9)	0.06
Vascular claudication	11 (22.4)	6 (17.1)	11 (20.2)	0.55
Alcoholism	3 (6.1)	10 (28.6)	8 (9.5)	0.27
BMI > 30	11 (22.4)	14 (40.0)	25 (29.8)	0.08
Stroke severity and stroke prediction scales				
NIHSS at admission	6	4	5	0.59
CHA_2DS_2-VASc (median)	4			
HAS-BLED (median)	2	1	1.5	0.01

Table 2. Incidence rates of first-ever AF and non-AF-related cardioembolic ischemic stroke in Joinville, Brazil, in 2015.

Variable	Men	Women	Total population
	Incidence (95% CI)	Incidence (95% CI)	Incidence (95% CI)
AF-related CE			
Age (years)			
< 55	–	0.01 (0.002–0.04)	0.016 (0.007–0.03)
55–64	0.26 (0.08–0.6)	0.09 (0.01–0.34)	0.17 (0.07–0.35)
65–74	0.60 (0.2–1.40)	0.48 (0.15–1.11)	0.53 (0.26–0.98)
75–79	1.42 (0.29–4.16)	1.23 (0.34–3.14)	1.31 (0.52–2.69)
≥ 80	3.25 (1.2–7.1)	4.79 (2.83–7.57)	4.28 (2.74–6.37)
Total	0.07 (0.04–0.11)	0.11 (0.08–0.16)	0.09 (0.07–0.12)
Adjusted Brazil*	–	–	0.08 (0.06–0.11)
Adjusted World†	–	–	0.10 (0.07–0.13)
Non-AF-related CE			
Age (years)			
< 55	0.12 (0.04–0.29)	0.11 (0.03–0.28)	0.12 (0.05–0.22)
55–64	0.47 (0.21–0.88)	0.23 (0.07–0.55)	0.34 (0.19–0.58)
65–74	0.12 (00.2–0.67)	0.19 (0.02–0.69)	0.16 (0.03–0.47)
75–79	1.42 (0.29–4.16)	–	0.56 (0.11–1.63)
≥ 80	0.54 (0.01–3.02)	1.33 (0.43–3.10)	1.07 (0.39–2.33)
Total	0.07 (0.04–0.11)	0.06 (0.03–0.10)	0.07 (0.05–0.09)
Adjusted Brazil*	–	–	0.05 (0.04–0.08)
Adjusted World†	–	–	0.07 (0.05–0.1)
All causes of CE			
Age (years)			
< 55	0.12 (0.04–0.29)	0.14 (0.05–0.32)	0.13 (0.06–0.23)
55–64	0.72 (0.40–1.21)	0.33 (0.13–0.68)	0.52 (0.32–0.80)
65–74	0.72 (0.26–1.56)	0.67 (0.27–1.38)	0.67 (0.37–1.18)
75–79	2.85 (1.04–6.19)	1.23 (0.34–3.14)	1.86 (0.89–3.43)
≥ 80	3.79 (1.52–7.81)	6.12 (3.88–9.18)	5.35 (3.61–7.64)
Total	0.14 (0.10–0.20)	0.17 (0.12–0.23)	0.16 (0.13–0.20)
Adjusted Brazil*	–	–	0.16 (0.13–0.20)
Adjusted World†	–	–	0.14 (0.11–0.17)

Rates per 1000 inhabitants * Adjusted by direct method to Brazilian population per the 2000 census; † Segi's world population. AF: atrial fibrillation; CE: cardioembolic stroke

for AF-related events, 0.07 (0.05–0.1) for non-AF-related events, and 0.14 (0.11–0.17) for all causes of CE stroke events. Incidence rates of AF and non-AF events were similar in men and women. In those over 80 years old, 24/49 (49%) occurred in AF-related patients, and only 6/35 (17.1%) occurred in non-AF-related patients. Among patients with AF-related events, the proportion increased progressively with age, ranging from 2% at < 55 years to 63% at > 75 years. On the contrary, among patients with non-AF-related events, 40% occurred at age 55-64 years and 26% at age > 75 years.

The diagnostic work-up of CE patients is shown in Table 3. In patients with AF-related events, 26/49 (53%) were chronic AF (known previously), 15/49 (30%) were paroxysmal AF and 6/49 (12%) were new AF. A 24-hour Holter monitoring period was carried out in 6/49 (12.2%) of the AF-related events and in only 1/35 (3%) of the non-AF-related events (Table 3). No patient had prolonged cardiac monitoring

(insertable, or by telemetry). In patients with non-AF events, 11/35 (31.4%) had dilated myocardiopathy, and 7/35 (20%) had chronic heart failure (Table 4).

The Figure shows functional outcomes. The 90-day outcomes were similar in both groups: 40% became dependent or died. Among AF-related events, four patients changed their address, and among non-AF-related events, we missed one patient. Worryingly, of 23 patients with known prior AF at hospital admission, who were followed for up to three months, two became dependent (mRankin of 3 to 5), and five died (mRankin of 6).

At hospital discharge, 37/49 (75%) with AF-related CE stroke were on anticoagulant prescriptions. Warfarin was more often indicated than the new anticoagulants (Table 5). Anticoagulant prescription was less indicated in non-AF-related CE stroke than in AF-related CE stroke (18/35 [51.4%] versus 12/49 [24.5%]; p = 0.01).

Table 3. Diagnostic work-up of atrial fibrillation (AF) and non-AF cardioembolic (CE) ischemic stroke.

Variable	AF (n = 49)	Non-AF (n = 35)	All CE (n = 84)
Cranial tomography	49 (100)	35 (100)	84 (100)
Brain magnetic resonance	9 (18.4)	2 (2.7)	11 (13.1)
Electrocardiogram	49(100)	35 (100)	84 (100)
Chronic AF	26 (53)	-	26 (30.9)
Paroxistic AF	15 (30.6)	-	15 (17.8)
New AF	6 (12.2)	-	6 (7.1)
Atrial flutter	2 (4)	-	2 (2.3)
24-h Holter	6 (12.2)	1 (2.9)	7 (8.3)
Transthoracic echocardiogram	49 (100)	35 (100)	84 (100)
Transesophageal echocardiogram	3 (6.1)	3 (8.6)	6 (7.1)
Carotid ultrasound	43 (87.8)	27 (77.1)	70 (83.3)
Transcranial Doppler	17 (34.7)	19 (28.6)	27 (32.1)
Electroencephalogram	4 (8.2)	0 (0)	4 (4.8)
Carotid angio-tomography	1 (2)	1 (2.9)	2 (2.4)
Carotid angio-MRI	2 (4.1)	6 (17.1)	8 (9.5)
Cerebral angio-MRI	1 (2)	0 (0)	1 (1.2)

Data are number of patients (%) unless otherwise indicated; MRI: magnetic ressonance imaging.

Table 4. Middle and high-risk emboligenic causes in non-atrial fibrillation-related cardioembolic (CE) stroke.

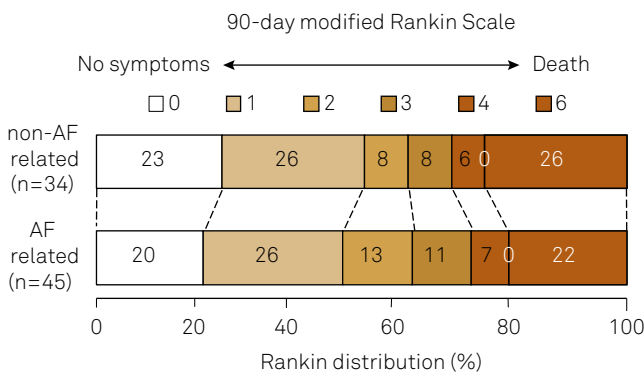| Non-AF-related CE	(n = 35)
High risk	
Mechanical valve	4 (11.4)
Myocardial infarction <4 weeks	1 (2.9)
Dilated myocardiopathy	11 (31.4)
Left ventricular akinesia	3 (8.6)
Atrial myxoma	2 (5.7)
Medium risk	
Mitral ring calcification	4 (11.4)
Mitral stenosis	1 (2.9)
FOP	1 (2.9)
Atrial flutter atrial	0 (0.0)
Chronic heart failure	7 (20.0)
Myocardial infarction >1 to 6 months	1 (2.9)

Table 5. Anticoagulation prescription at hospital discharge in patients with atrial fibrillation and non-atrial fibrillation cardioembolic ischemic stroke in Joinville, 2015.

Anticoagulated	AF (n = 49)	Non- AF (n = 35)	p- value
Warfarin	26 (53.1)	15 (42.9)	0.35
Femcoprumon	1 (2.0)	0 (0.0)	1.00
Apixaban	3 (6.1)	0 (0.0)	0.26
Rivaroxaban	4 (8,2)	0 (0.0)	0.13
Dabigatran	3 (6.1)	1 (2.9)	0.63
Enoxaparin sodium	0 (0)	1 (2.9)	0.41
Not anticoagulated	12 (24.5)	18 (51.4)	0.01

90-day modified Rankin Scale

Figure. Modified Rankin scale scores at 90-days between non-AF related and AF related cardioembolic ischemic stroke in Joinville, 2015; AF: atrial fibrillation; 0 to 1: very favorable outcome, 0 to 2: functional independence, 3 to 5: functional dependence and 6: death. Values inside each box were proportions (%).

DISCUSSION

The age-adjusted incidence per 1,000 person-years was 0.10 (95% CI, 0.07–0.13) for AF-related events; 0.07 (0.05–0.1) for non-FA-related events; and 0.14 (0.11–0.17) for all causes of CE stroke events. At hospital discharge, three quarters of AF-related events were on anticoagulant prescriptions, mainly warfarin. After three months, 60% were functionally independent, 18% were dependent and 22% had died. These outcomes were the same for AF-related and non-AF-related events.

Few studies have published the incidence of AF-related stroke specifically. In Dublin, the crude incidence of first-ever AF-associated ischemic stroke was 0.42/1000 person-years (95% CI = 0.35–0.51) in 2005-2006[23]. In Oxford, the crude AF-related incidence was 0.41 (0.36–0.45) events over 10 years (2002-2012).[7] These rates are three times higher than our findings. Could these differences be explained by life expectancy? In the UK, for example, 51% (272/454) of AF-related events occurred in people 80 years or older, whereas in our sample, 35.7% (30/84) were in the same age

strata. Distinct socio-economic and ethnic profiles and diagnostic work-up (i.e., proportion of undetermined ischemic strokes) could also explain these diferences[1,9,24].

Unfortunately, many CE events could have been prevented. The proportion of patients with ischemic stroke and known prior AF who were on premorbid oral anticoagulation were observed in some population-based studies[3,7,25]. In Adelaide, 57/81 (70%) of patients with CE events had known previous AF, and 32/57 (56%) of those were not anticoagulated[3]. In Oxford, 189/383 (49%) of AF-related events occurred in non-anticoagulated patients with known prior AF[7]. In Dublin, 63/87 (72.4%) were not on warfarin therapy at stroke onset[23]. In 2000, we reported that 14/21 (66%) of AF-related events occurred in non-anticoagulated patients with known prior AF in Joinville[26]. In the current sample, 15 years later, 73% (19/26) with known prior AF were not anticoagulated.

It is interesting to note that three quarters had a previous high risk of stroke on the CHA_2DS_2VASc scale (score $\geq$ 3)[18] although more than three quarters had a low risk of bleeding on the HAS-BLED scale (score < 3)[19]. Of concern, a third of these died within three months of becoming disabled. These findings reflect an alarming and sustained poor knowledge of the primary prevention benefits of anticoagulation for AF in our setting, as the use of warfarin or new oral anticoagulants reduces the relative risk of stroke recurrence by 60%-70%[25].

The 30-day patient fatality was 22.5% for AF-related events and 26.5% for non-AF events. These findings are similar to those reported in Adelaide (23%)[3], Rochester (30.3%)[27] and Iquique (28%)[28]. In contrast, the Dublin study reported 23.1% for AF-related stroke and 12.1% for non-AF-related stroke[23].

The major strength of this study is the population-based design[12]. To define the final ischemic stroke subtype (TOAST classification), all CE stroke patients had cranial CT, ECG and echocardiogram; and more than 80% had carotid ultrasound. The final diagnostics of AF-related and non-AF-related events were double-checked. However, our study has several limitations. It is possible that our CE sample could be underestimated because screening for paroxysmal and new AF events is not ideal. Only 12% of patients with AF-related events and 3% of those with non-AF-related events had a 24-hour Holter recording. Less than 10% had transesophageal ECG. No patient had prolonged cardiac monitoring (insertable or by telemetry). Our registry does not perform "hot pursuit"[2], which might result in underestimates of the overall stroke incidence. Although reliable and validated[21], functional assessments were performed by telephone, which is less ideal than face-to-face interviews. However, we understand that information bias in our sample is unlikely because our register had a trained nursed who used a validated scale for Rankin assessment by telephone call[29].

In conclusion, the incidence of first-ever AF-related CE in our setting is lower than in other population-based studies. A third of our sample had previously-known AF. Of those, most had a high risk of embolization ($CHA_2DS_2VASc \geq 3$) and a low bleeding risk (HAS-BLED score < 3). A third of AF-related and non-AF-related stroke patients had a poor outcome after three months. These findings might be useful for primary prevention policies. Further studies of CE ischemic stroke incidence in our setting could clarify the trends we observed.

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