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# Infective endocarditis is associated with worse outcomes in stroke: A Thailand National Database Study

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## Abstract

**Background:** There is lack of data on the association between infective endocarditis (IE) and outcomes of mortality and complications in stroke. We aimed to compare characteristics and outcomes of stroke patients with and without IE.

**Methods:** We retrospectively examined the above association using data obtained from an insurance database which covers ~75% of the Thai population. All hospitalised strokes between 8 January 2003 and 31 December 2013 were included in the current study. Characteristics and outcomes were compared between stroke patients with or without IE, and then between two main stroke types. Multiple logistic regression models including propensity score-matched analyses were constructed to assess study outcomes controlling for age, sex, stroke type and comorbidities.

**Results:** A total of 590 115 stroke patients (mean (SD) age = 64.2 ± 13.7 years; ischaemic = 51.7%; haemorrhagic = 32.6%; undetermined = 15.7%) were included, of whom 2129 (0.36%) had stroke associated with IE. After adjustment, we found that IE was significantly associated with the following complications: arrhythmias (adjusted odds ratio (95% CI) 6.94 (6.29-7.66)), sepsis (1.24 (1.01-1.52)), pneumonia (1.34 (1.17-1.53)), respiratory failure (1.43 (1.24-1.66)) and in-hospital mortality (1.29 (1.13-1.47)) (P for all <.001). Patients with haemorrhagic stroke with IE had poorer outcomes for in-hospital mortality and respiratory failure compared with their counterparts with ischaemic stroke. Propensity score-matched analysis showed similar results.

**Conclusions:** Our results suggest that stroke patients with IE differ from that of the general stroke population and these patients have worse outcomes. Future studies are needed to determine the best treatment strategies for stroke patients with IE.

# 1 | INTRODUCTION

Infective endocarditis (IE) remains a significant burden in low- and middle-income countries, particularly in regions with high incidence of rheumatic heart disease. Though relatively uncommon in developed countries, IE is of importance because of the high mortality rate associated with the condition—up to 40% of patients will die within 5 years of diagnosis.[1-6] Furthermore, IE has become a condition that affects all ages; trends in incidence show an increase in the age of patients developing IE over the last five decades.[7]

Stroke is a recognised serious complication of IE,[8] typically because of dissemination of multiple emboli from an endocardial vegetation. Studies have reported that stroke accounts for as much as 16.9% of the complications of IE.[9,10] While variations in the prevalence of stroke in IE have been identified across different regions in the world (as well as between different regions of the same country),[6] studies have found that moderate strokes are associated with poorer prognosis and higher mortality in patients with IE.[11]

To the best of our knowledge, there has been no literature specifically regarding clinical characteristics and outcomes (including common stroke complications) in stroke patients with IE. Because of the fact IE is a relatively uncommon cause of stroke in western countries, there is a lack of understanding regarding the prognosis of stroke in people with IE.

Using the Thailand National Insurance Database of the Universal Coverage Scheme, our study aims were: (a) to compare characteristics of stroke patients with and without IE; (b) to compare acute stroke outcomes (in-hospital mortality, long length of stay (>14 days), cardiac and non-cardiac complications following stroke in patients with and without IE; and (c) to compare the outcomes of patients with IE between ischaemic and haemorrhagic stroke admitted to secondary care in Thailand.

## 2 | METHODS

### 2.1 | Study design

We used data from the Universal Coverage Health Security Insurance Scheme Database which includes routinely collected consecutive admission data representative of all hospital admissions of stroke in Thailand. The Thai population is covered by three insurance schemes. The Civil Servant Benefit System covers government employees and their dependents (≈7% of the population). The Social Security scheme covers private sector employees (≈13% of the population). The Universal Coverage Health Security Scheme is a basic health insurance scheme covering the remaining ~75% of the population.[12]

The study participants comprised of a cohort of adult Thai patients admitted to provincial and large community hospitals in Thailand between January 2003 and December 2013. We excluded those who are over 100 years as they only constitute 0.00016% of

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**What's known**

- Infective endocarditis (IE) remains a significant burden in low- and middle-income countries with high incidence of rheumatic heart disease and stroke is a recognised serious complication of IE.
- Because of the fact IE is a relatively uncommon cause of stroke in western countries, there is a lack of understanding regarding the prognosis of stroke in people with IE.

**What's new**

- Our analysis of 590 115 stroke patients in the Thailand National Insurance Database found that 0.36% (n = 2129) had stroke associated with IE.
- We found that IE was significantly associated with arrhythmias (OR 6.94 (6.29-7.66)), sepsis (OR 1.24 (1.01-1.52)), pneumonia (OR 1.34 (1.17-1.53)), respiratory failure (OR 1.43 (1.24-1.66)) and in-hospital mortality (OR 1.29 (1.13-1.47)).
- Patients with haemorrhagic stroke with IE had poorer outcomes for in-hospital mortality and respiratory failure compared with their counterparts with ischaemic stroke.

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the sample and are also most likely to be an error of data entry in most patients. Diagnosis of stroke and IE was identified from ICD coding on reimbursement forms (ICD10; I60-I64 for stroke and I38 for IE). In Thailand, diagnosis of stroke is made by attending clinical teams based on clinical features and investigation findings including brain imaging (since 2009 all received a head CT scan in line with National Guidelines). Demographic and clinical data were obtained from reimbursement forms using ICD codes on an annual basis. Stroke types were categorised as haemorrhagic (I61, I62), ischaemic (I63) or stroke of undetermined pathology (I64). Our study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the Ethics Committee in Human Research, Khon Kaen University, Khon Kaen, Thailand. The description of the cohort has also been described previously.[13,14]

### 2.2 | Outcome measures

Serious common poststroke complications were examined as primary outcomes in this study with their relationship with in-hospital mortality and length of in-hospital stay. Data on poststroke complications and co-morbid conditions were obtained from the ICD codes (Table S1). Outcomes of interest such as cardiac complications, in-hospital mortality and length of stay were preselected and other complications were chosen based on their common occurrence.

## 2.3 | Statistical analysis

Statistical analyses were performed using SPSS for Mac version 24.0 (SPSS Inc, Chicago, IL, USA). Descriptive statistics were compared by IE status and stroke type. Logistic regression models were constructed to examine the association between IE and selected outcomes following stroke. The selected outcomes of interest were cardiac complications—MI, cardiac arrest, arrhythmias—and non-cardiac complications of sepsis, pneumonia, respiratory failure and convulsions. We also examined the in-hospital mortality and likelihood of long length of stay (>14 days). The reference category for these regression models was stroke patients with no IE. Unadjusted and three adjusted models with incremental adjustments (models A-C) were carried out to examine the associations for complications (see Table 3 footnotes). For the outcome of long length of stay, to gain deeper insight and better understanding of the relationships, analyses were carried out for those who died as an inpatient and those who were discharged alive. Matched propensity score analyses based on factors in Model C of logistic regression were carried out to attempt to eliminate the possibility that the differences observed were because of inadequately controlled co-variates.

To better understand the impact of some selected major prognostic factors, the likelihood of aforementioned outcomes was examined using logistic regression models stratified according to age group (18-64 and 65-100), stroke type (ischaemic, haemorrhagic and undetermined stroke type) and sex. We also performed subgroup analysis comparing two major stroke subtypes (using ischaemic stroke as reference) in those with IE only.

## 3 | RESULTS

A total of 590 115 stroke patients admitted to secondary care under Universal Coverage scheme in Thailand between 8 January 2003 and 31 January 2013 were included. Sample mean age (SD) was 64.2 (±13.7) years and the prevalence of IE was 0.36% (N = 2129). Males constituted 55% of the sample and ischaemic strokes were the most common stroke subtype (51.7%). Haemorrhagic stroke and undetermined stroke types made up 32.6% and 15.7% of the sample, respectively. Characteristics comparison according to presence or absence of IE is presented in Table 1. On average, patients with IE were slightly younger (4.4 years) and a greater proportion was female ($P < .0001$). The most common type of stroke in both groups was ischaemic stroke (8% higher in IE); however haemorrhagic stroke was 1.55 times more common in stroke patients without IE ($P < .0001$). The prevalence of heart failure was almost five times greater in the IE group and other coagulation defects were almost 10 times as common ($P < .0001$). Stroke patients without IE were almost two times as likely to have cardiovascular risk factors such as dyslipidaemia and type II diabetes mellitus ($P < .0001$). The characteristics according to stroke subtype are shown in Table S2.

Common complications of stroke in this cohort were MI, cardiac arrest, arrhythmias, sepsis, pneumonia, respiratory failure and

**TABLE 1** Characteristic comparison between 590 115 stroke patients with and without infective endocarditis admitted to secondary care in Thailand (2003-2013)

| | Infective endocarditis (%) | No infective endocarditis (%) | P-value |
|---|---|---|---|
| Total N | 2129 (0.4) | 587 986 (99.6) | |
| Mean age (SD) | 59.8 (15.6) | 64.2 (13.7) | <.0001 |
| Sex | | | |
| Male | 866 (40.7) | 323 551 (55.0) | |
| Female | 1263 (59.3) | 264 435 (45.0) | |
| Stroke type | | | |
| Ischaemic | 1268 (59.6) | 303 543 (51.6) | |
| Haemorrhagic | 449 (21.1) | 192 063 (32.7) | |
| Undetermined | 412 (19.4) | 92 380 (15.7) | <.0001 |
| Comorbidities | | | |
| RMVD | 55 (2.6) | 5394 (0.9) | <.0001 |
| CAD | 98 (4.6) | 16 652 (2.8) | <.0001 |
| Hypertension | 515 (24.2) | 264 393 (45) | <.0001 |
| Heart failure | 153 (7.2) | 8660 (1.5) | <.0001 |
| Dyslipidaemia | 210 (9.9) | 117 145 (19.9) | <.0001 |
| Anaemia | 179 (8.4) | 31 428 (5.3) | <.0001 |
| Other coagulation defects | 146 (6.9) | 4386 (0.7) | <.0001 |
| Type II diabetes mellitus | 180 (8.5) | 99 116 (16.9) | <.0001 |
| CKD | 62 (2.9) | 18 894 (3.2) | 0.431 |
| Alcohol-related disorders | 11 (0.5) | 9185 (1.6) | <.0001 |
| Age-related physical debility | 7 (0.3) | 3476 (0.6) | .115 |
| COPD | 42 (2.0) | 11 441 (1.9) | .928 |

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; RMVD, rheumatic mitral valve disease; SD, standard deviation.

convulsions, and were therefore selected as outcomes of interest (Table 2). Overall, stroke complications were more prevalent in the IE patients, although there was no statistically significant difference in the rates of convulsions between two groups ($P = .35$). Arrhythmias were 5.5 times more common in the IE patients. MI was two times as common in the IE group. Cardiac arrest, sepsis, pneumonia and respiratory failure were all more prevalent in the IE patients. In-hospital mortality was marginally greater in the IE group. There was no statistically significant difference in length of inpatient stay ($P = .56$).

Table 3 displays odds ratios and corresponding 95% confidence intervals for outcomes of stroke in patients with IE compared with those without. After full adjustment, IE was significantly associated with greater odds of arrhythmias, sepsis, pneumonia, respiratory failure and in-hospital mortality. IE was less likely to be associated with convulsions (OR 0.72; 0.52-0.99). Arrhythmias were almost

seven times greater in odds of occurring in the stroke patients with IE (OR 6.94; 6.29-7.66). IE was not significantly associated with having a long length of stay.

**TABLE 2** Comparison of outcomes following stroke in 590 115 patients (all ages) with and without infective endocarditis admitted to secondary care in Thailand (2003-2013)

| Outcome | Infective endocarditis (%) | No infective endocarditis (%) | P-value* |
|---|---|---|---|
| Total N | 2129 (0.4) | 587 986 (99.6) | |
| Serious complications | | | |
| MI | 26 (1.2) | 3383 (0.6) | <.0001 |
| Cardiac arrest | 36 (1.7) | 6112 (1.0) | .0030 |
| Arrhythmias | 764 (35.9) | 38 293 (6.5) | <.0001 |
| Sepsis | 101 (4.7) | 18 908 (3.2) | <.0001 |
| Pneumonia | 272 (12.8) | 56 086 (9.5) | <.0001 |
| Respiratory failure | 231 (10.9) | 41 965 (7.1) | <.0001 |
| Convulsions | 33 (1.6) | 10 720 (1.8) | .3470 |
| In-hospital mortality | 314 (14.7) | 69 287 (11.8) | <.0001 |
| Length of inpatient stay | | | .5560 |
| ≤14 d | 1941 (91.2) | 533 891 (90.8) | |
| >14 d | 188 (8.8) | 54 095 (9.2) | |

Abbreviation: MI, myocardial infarction.

*Data are presented as median (IQR) for continuous data (length of stay) and number (%) for categorical data (in-hospital mortality and complications).

Propensity score-matched analyses showed similar results. It also showed that IE was associated with ~fourfolds greater odds of in-hospital mortality (OR 4.80;3.70-6.24) and arrhythmias (OR 4.06 (3.37-4.75)) as well as significantly increased odds of MI and cardiac arrest (P < .0001) and of having a long length of stay.

Table S3 stratifies the analysis presented in Table 3 according to key characteristics (age, stroke type and sex) to compare the impact of these variables on the likelihood of in-hospital mortality and having a long length of stay. In ischaemic stroke, being a patient with IE was associated with the greatest increase in odds of in-hospital mortality. It was also associated with increased odds of having a long length of stay. Being a female stroke patient with IE had greatest increased odds of in-hospital mortality when compared with stroke patients without IE (OR 1.57 (1.34-1.85)).

Table S4 stratifies as in Table S3 comparing the impact of the specific patient characteristics on the likelihood of the development of certain common stroke complications in the stroke patients with IE compared with those without IE. IE was associated with increased odds of developing arrhythmias across all stroke subtypes but particularly high odds were in association with haemorrhagic stroke. Ischaemic stroke in association with IE was associated with the greatest increase in odds of development of respiratory failure. Female patients who also had IE had greatest increased odds in the development of pneumonia (1.52; 1.28-1.80) and respiratory failure (1.90; 1.59-2.27) when compared with stroke patients without IE. Male patients who also had IE had greatest increased odds in the development of arrhythmias (8.87; 7.60-10.35).

Table 4 shows the frequency distribution of complications by IE status and fully adjusted results of regression analyses that compare

**TABLE 3** Odds ratios and corresponding 95% confidence intervals from binary logistic regression analyses to examine outcomes in stroke in 2129 patients with infective endocarditis using 587 986 patients without infective endocarditis as the reference category in Thailand (2003-2013). Odds ratio (95% confidence interval)

| Outcome | Unadjusted[*,a] | Model A[b] | Model B[c] | Model C[d] | Propensity Score Matched Analyses[e] |
|---|---|---|---|---|---|
| MI | 2.14 (1.45-3.15) | 2.25 (1.53-3.32) | 2.20 (1.49-3.24) | 1.46 (0.98-2.17) | 2.01 (1.03-3.93) |
| Cardiac arrest | 1.64 (1.18-2.28) | 1.57 (1.13-2.18) | 1.78 (1.28-2.48) | 1.34 (0.96-1.87) | 2.27 (1.26-4.11) |
| Arrhythmias | 8.04 (7.35-8.79) | 8.91 (8.13-9.77) | 8.53 (7.77-9.37) | 6.94 (6.29-7.66) | 4.06 (3.47-4.75) |
| Sepsis | 1.50 (1.23-1.83) | 1.54 (1.26-1.88) | 1.61 (1.31-1.97) | 1.24 (1.01-1.52) | 1.99 (1.42-2.79) |
| Pneumonia | 1.39 (1.22-1.58) | 1.54 (1.36-1.75) | 1.68 (1.47-1.91) | 1.34 (1.17-1.53) | 1.74 (1.42-2.14) |
| Respiratory failure | 1.59 (1.38-1.82) | 1.60 (1.39-1.84) | 1.90 (1.65-2.20) | 1.43 (1.24-1.66) | 2.23 (1.77-2.83) |
| Convulsions | 0.86 (0.63-1.19) | 0.85 (0.62-1.18) | 0.85 (0.62-1.17) | 0.72 (0.52-0.99) | 0.80 (0.50-1.27) |
| In-hospital mortality | 1.30 (1.15-1.46) | 1.29 (1.14-1.45) | 1.69 (1.49-1.92) | 1.29 (1.13-1.47) | 4.80 (3.70-6.24) |
| Long length of stay (>14 days) | 0.96 (0.82-1.11) | 0.97 (0.84-1.13) | 1.14 (0.98-1.32) | 0.95 (0.81-1.11) | 1.25 (1.00-1.56) |
| Living patients long length of stay (>14 d) | 0.97 (0.82-1.14) | 0.96 (0.81-1.14) | 1.17 (0.99-1.39) | 0.96 (0.81-1.14) | |
| Deceased patients long length of stay (>14 d) | 0.83 (0.59-1.17) | 0.94 (0.67-1.32) | 0.84 (0.60-1.19) | 0.84 (0.59-1.20) | |

[a]Unadjusted.

[b]Model A = adjusted for age, sex and year of secondary care admission.

[c]Model B = adjusted for age, sex, year of secondary care admission and stroke type.

[d]Model C = adjusted for age, sex, year of secondary care admission, stroke type and comorbidities.

[e]Propensity score-matched analyses = based on factors in Model C.

**TABLE 4** Comparison of outcomes in stroke in 1717 people with infective endocarditis with ischaemic stroke or haemorrhagic stroke admitted to secondary care in Thailand (2003-2013)*

| Outcome | Ischaemic stroke n (%) | Haemorrhagic stroke n (%) | P-value | OR (CI)[a] |
|---|---|---|---|---|
| Total N | 1268 (73.8) | 449 (26.2) | | |
| Serious complications | | | | |
| MI | 15 (1.2) | 6 (1.3) | .799 | 1.07 (0.37-3.16) |
| Cardiac arrest | 22 (1.7) | 10 (2.2) | .508 | 0.91 (0.36-2.32) |
| Arrhythmias | 524 (41.3) | 105 (23.4) | <.0001 | 0.46 (0.35-0.61) |
| Sepsis | 68 (5.4) | 24 (5.3) | .989 | 0.75 (0.43-1.31) |
| Pneumonia | 187 (14.7) | 53 (11.8) | .122 | 0.74 (0.51-1.06) |
| Respiratory failure | 136 (10.7) | 78 (17.4) | <.0001 | 1.60 (1.13-2.27) |
| Convulsions | 28 (2.2) | 6 (1.3) | .254 | 0.50 (0.18-1.41) |
| In-hospital mortality | 157 (12.4) | 133 (29.6) | <.0001 | 2.55 (1.90-3.43) |
| Length of in-patient stay | | | .026 | |
| >14 d | 117 (9.2) | 58 (12.9) | | 1.21 (0.83-1.78) |

Abbreviation: MI, myocardial infarction.

*Data are presented as median (IQR) for continuous data (length of stay) and number (%) for categorical data (in-hospital mortality and complications).

[a]Odds ratios and corresponding 95% confidence intervals from binary logistic regression analyses to examine outcomes in 449 haemorrhagic stroke patients with infective endocarditis using 1268 ischaemic stroke patients as a reference category in Thailand (2003-2013). Adjusted for age, sex, year of hospital admission and comorbidities.

the odds of outcomes in haemorrhagic stroke patients with IE compared with their counterparts with ischaemic stroke. Arrhythmias were almost double as common in ischaemic stroke, whereas in-hospital mortality was over two times as common (2.55; 1.90-3.43) in the haemorrhagic strokes (P < .0001 for both). Patients with haemorrhagic stroke also had increased odds of developing respiratory failure (1.60; 1.13-2.27).

## 4 | DISCUSSION

There are several key findings to this national study of IE and stroke from a non-Western country. First, IE in the context of stroke is pro-arrhythmic as it is associated with a sevenfold increase in odds of arrhythmias compared with non-IE patients. Secondly, not only does it increase in-hospital mortality but IE also increases non-cardiac pathology such as sepsis, pneumonia and respiratory failure compared with patients without IE. Third, among stroke patients, patients with IE are younger, more likely to be female with ischaemic stroke type and have rheumatic mitral valve disease, coronary artery disease, heart failure, anaemia and coagulation defects. Fourth, patients with haemorrhagic stroke and IE had poorer outcomes for in-hospital mortality and respiratory failure compared with their counterparts without ischaemic stroke. These findings suggest that IE as associated with worse prognosis among stroke patients and this high-risk group may require early identification within the general stroke cohort, escalation to high dependency or critical care areas if they are found to be at risk of deterioration and urgent management.

To date, most literature surrounding IE and stroke largely focusses on neurological outcomes of IE and does not address the more specific question of the prognosis in stroke in patients with IE. They report that neurological complications, particularly when they are symptomatic, are associated with poorer outcomes such as higher rates of in-hospital mortality. Consequently, other literature on the topic concerns examining appropriate indications for and timing of cardiac surgery to improve prognosis in IE patients, in part to avoid further cerebral events.[11,15,16] To our knowledge, this study provides the first analyses to date specifically on the clinical characteristics and outcomes (including common stroke complications) in stroke patients with IE. This may help allow for better insight into identifying stroke patients at greatest risk of severe complications. The strengths of our analyses include the national, unselected large sample size that is representative of a country where the rates of IE are significant with prospective identification of participants.

In line with previous literature on the characteristics of patients with IE, the stroke patients with IE were younger than those without. However, contrary to these reports, our study found a greater proportion of stroke patients with IE were female.[17,18] Consistent with the morbidity profile of older individuals in Asia, traditional stroke risk factors such as diabetes mellitus and hypertension were more common in the patients without IE.[19-21] We demonstrate a higher rate of poststroke complications in patients with IE and, to our knowledge, are the first group to specifically report this. IE had a large impact on the likelihood of developing arrhythmias and was associated with greater prevalence of serious complications such as sepsis, pneumonia and in-hospital mortality.

In line with current statistics on common stroke types in Asia, patients with IE also had a higher proportion of ischaemic stroke and they had higher proportion of cardiac comorbidities. There are several plausible mechanisms by which ischaemic stroke is

common in patients with IE; embolisation of infective or platelet thrombi from a cardiac vegetation or underlying socioeconomic and cardiovascular risk factors such as smoking, excessive alcohol consumption and poor diet all increase the risk of ischaemic stroke in the population and so may influence the prevalence of stroke subtype.[22-24]

Interestingly, among the stroke patients with IE, a lower prevalence of haemorrhagic stroke than would be expected of an Asian population was observed.[25-27] We postulate that this may be because of the fact that IE patients are younger and that increased rates of haemorrhagic stroke in the Asian population tend to be linked to high salt diet with resultant hypertension which is common with older age.[21,28-31]

There was a greater proportion of stroke patients with IE who developed cardiac arrest and had a MI compared with stroke patients who did not have IE. Acute coronary syndromes have previously been reported as being complications of IE, and may relate to embolic phenomena, particularly from aortic valve endocarditis.[32] The results from the propensity score-matched analyses mirror the results from the regression analysis, further strengthening the evidence suggesting that IE is associated with worse outcomes in stroke. There was no significant result associated with length of inpatient stay. Several factors are involved in predictors of length of inpatient stay in stroke patients including severity of stroke, co-morbid conditions and nutritional status[33-35] and so the findings observed may be explained by unmeasured confounders which are important for this specific outcome. Furthermore, the association between increased in-hospital mortality in stroke patients and the female sex has previously been described.[36,37] This paper serves to further emphasise the importance in sex-specific differences in the outcomes of stroke related to certain comorbidities—in this instance, IE.

Because of the large sample, we could examine the impact of IE in stroke patients comparing the characteristics and outcomes of two main stroke subtypes. In keeping with literature on stroke prognosis, patients with IE and haemorrhagic stroke had worse in-hospital mortality. We also identified that they had higher odds of respiratory failure compared with those with ischaemic stroke. The reason is unclear and beyond the remit of the current study although this may be related to stroke severity.

To date, most literature surrounding IE and stroke largely focusses on neurological outcomes of IE and does not address the more specific question of the prognosis in stroke in patients with IE. They report that neurological complications, particularly when they are symptomatic, are associated with poorer outcomes such as higher rates of in-hospital mortality. One study did suggest that IE-related stroke had a favourable prognosis with regard to long-term survival and neurological recovery.[38]

Our study has some limitations. First, we relied on ICD coding for diagnosis of stroke, comorbidity and complication data, including IE. Second, we did not have data on the medical therapies used, which may affect stroke outcome. However, there is evidence to suggest that pre-existing anticoagulation does not have effect on stroke,

cerebrovascular haemorrhage or mortality in patients with left-sided IE at 10 weeks.[39] Thirdly, we were unable to study mild strokes that were not admitted to hospital or very severe strokes where the patient died before being admitted. Nevertheless, truncation of distribution would only be likely to attenuate the results. Because of the nature of large-scale epidemiological data, detailed information on heart valve lesions (size, location and infecting organism), cardiac surgery, stroke severity (as classified by the NIH Stroke Score) and whether the patients had active IE at the time of the stroke or were diagnosed thereafter has not been included. These factors have important implications on outcomes in stroke patients and would be valuable to examine in any future study specifically regarding outcomes in stroke patients with IE.[11] Another limitation is that we lack data on microbiological investigations, cardiology investigations and cardiac surgery which may be relevant to IE. Finally, we did not have information on the temporal relationship between IE and stroke. It has been suggested that the association between IE and stroke is made close together in time but the period of heightened stroke risk becomes apparent several months before diagnosis of IE and lasts several months after.[40]

However, despite these limitations, this study provides important insights into the prognosis of stroke patients with IE for the first time in literature. We describe detailed information on the rates of common stroke complications and important outcomes such as in-hospital mortality and length of stay in IE patients who developed stroke. The use of large data based on unselected patient population through record linkage allows us to robustly control case-mix with a particular focus on a comprehensive list of comorbidities. Indeed, this approach has formed the basis of better understanding of epidemiology and outcomes in relatively rare conditions. It overcomes selection bias which is the major limitation of small-scale clinical studies and randomised trials.

In conclusion, the findings confirm that the characteristics of stroke patients with IE are different from those in the general stroke population and that the prevalence, and in some patients, risk of certain concomitant comorbidities and poststroke complications are greater. Though certain findings may seem self-explanatory that having one serious condition (IE) would make the prognosis in another serious condition (stroke) worse, this study nevertheless contributes vital information, important in evidence-based medicine, to help clinicians in ensuring extra-care that should be given to patients with IE who have stroke. Although IE is a rare condition, it is associated with high morbidity and mortality and as such is important for the clinician to recognise and effectively manage what is a challenging condition with poor prognosis. Future work should focus on fully establishing risk factors and mechanisms of stroke in IE, and developing the best treatment strategies for stroke patients with IE.

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## DISCLOSURES

The authors have declared no conflicts of interest for this article.

## AUTHOR CONTRIBUTIONS

PKM conceived the study and is the guarantor. ST co-ordinated the data acquisition and obtained ethical approval. ABC and JHBS cleaned the data. PKM and KAR formulated the analysis plan. KAR analysed the data and drafted the paper. All the authors contributed in the writing of the paper.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.