Impact of Heart Failure on Stroke Mortality and Recurrence

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ABSTRACT

Objective: We aimed to examine the impact of HF on stroke mortality and recurrence (in-hospital and post-discharge) in a national stroke cohort from Thailand.

Methods: We utilised a large insurance-based database including all stroke admissions in the public health sector in Thailand between 2004 and 2015. Logistic and Royston-Parmar regressions were used to quantify the effect of HF on in-hospital and long-term outcomes, respectively. All models were adjusted for age, sex and and co-morbidities and stratified by stroke type: Acute Ischaemic Stroke (AIS) or Intracerebral Haemorrhage (ICH). Multi-state models were constructed using flexible survival techniques to predict the impact of HF on the disease course of a stroke patient (baseline-(recurrence)-death). Only first-ever cases of AIS or ICH were included in the multi-state analysis.

Results: 608,890 patients (mean age 64.29±13.72 years, 55.07% men) were hospitalised (370,527 AIS, 173,236 ICH and 65,127 Undetermined pathology). There were 398,663 first-ever AIS and ICH patients. Patients were followed up for a median (95%CI) of 4.47 years (4.45 – 4.49). HF was associated with an increase in post-discharge mortality in AIS (HR[99%CI]=1.54[1.48-1.61]) and ICH (2.10[1.47-3.00]). HF was associated with AIS recurrence (1.46 [1.08-1.98]) in those surviving beyond 8 months, whilst ICH recurrence was only significantly increased within first 18 months (2.01 [1.19-3.40]).

Conclusions: HF increases the risk of mortality in both AIS and ICH. We are the first to report on high-risk periods of stroke recurrence in HF patients with ICH. Specific targeted risk reduction strategies may have significant clinical impact for mortality and recurrence in stroke.

Key Words: Heart Failure, Cerebrovascular Disorders, Brain Infarction, Cerebral Haemorrhage

KEY QUESTIONS

What is already known about this subject?

- Heart failure is associated with higher mortality and recurrence rates after ischaemic stroke
- Previous literature results are based solely on Western populations

What does this study add?

- This is the first study to examine this relationship in an Asian stroke population
- Heart failure predicts higher mortality outcomes not only in ischaemic, but also in haemorrhagic stroke patients
- Heart failure is only associated with higher recurrence rates in the short-term follow-up for both stroke types

How might this impact on clinical practice?

- Clinicians should be aware that both ischaemic and haemorrhagic stroke patients with heart failure are at higher risk of both mortality and recurrence in the short-term (up to 2 years)
- This study should be replicated in other Asian populations

INTRODUCTION

Heart failure (HF) is a recognized risk factor for stroke incidence. The proposed mechanisms underlying the association between HF and increased risk of acute ischemic stroke (AIS) include thromboembolism, cerebral hypoperfusion and small vessel endothelial damage [1]. The association between HF and ICH is less clearly understood, but may relate to antithrombotic therapy being administered in patients with HF, particularly in those with ischaemic cardiomyopathy or AF [2].

Given the increased stroke incidence in HF patients, hypotheses regarding the influence of pre-existing HF on acute stroke outcomes have been formulated [3]. Previous studies have mainly analysed the association between prevalent HF and post-AIS outcomes, suggesting that it may be associated with higher mortality, longer in-hospital stay and higher disability and recurrence rates [1, 4-8]. Nevertheless, there have been no studies evaluating the impact of HF on the outcomes of intracerebral haemorrhage (ICH).

In the current study, we sought to determine impact of HF on in-hospital and long-term outcomes (mortality and stroke-specific recurrence) in both major stroke subtypes (AIS and ICH) using a large unselected cohort of stroke patients. Identification of HF as a risk factor for stroke mortality and recurrence may drive further research for the identification and testing of targeted interventions in this population.

METHODS

Data acquisition, case ascertainment and variable coding

We utilised a large observational cohort of consecutively admitted stroke patients from Thailand, drawn from the Universal Coverage (UC) Health Insurance Database. Details regarding the health insurance systems in Thailand can be found in our previous reports [9, 10]. Eligible patients were selected based on the primary diagnosis ICD10 (*International Classification of Disease, tenth revision*) code recorded in the database. All patients covered by the basic health insurance system ever admitted between October 2004 and September 2015 with a diagnosis of stroke (ICD10 codes I61 (intracerebral haemorrhage), I63 (cerebral infarction), I64 (stroke of undetermined pathology)) were included in this study. Pre-existing co-morbidity, demographic and clinical data were extracted from insurance reimbursement forms using ICD10 codes, detailed in **Supplementary Table 1.**

Further admissions with a primary diagnosis of stroke or heart failure (ICD10) and the vital status (date of death if applicable) were recorded. A recurrent stroke event during the follow-up was extracted only if the primary diagnosis of this admission matched the one of the index stroke. In order to account for any new HF diagnoses, we also assessed subsequent hospital admissions, for any changes in the HF comorbidity status. Our study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee in Human Research, Khon Kaen University, Khon Kaen, Thailand.

Inclusion criteria

Inclusion criteria, outcomes of interest (mortality and stroke recurrence) and selection of study variables were all determined *a-priori*. A total of 615,758 of stroke patients were admitted with primary diagnosis of stroke in the database. After excluding patients younger than 18 (n=1427) or older than 100 (n=43) and those with a missing post-discharge data (n=5419), a total of 608,890 acute stroke patients were included.

For the outcome of stroke recurrence, a further 81,530 patients with prevalent stroke (ICD10 I61, I63, I64) were excluded as well as 128,697 stroke patients who were diagnosed with a stroke of undetermined pathology on their index admission, yielding a cohort of 398,663 first-ever AIS and ICH patients.

Statistical Analysis

All analyses were performed using Stata 14.2 SE (StataCorp 2015), Stata Statistical Software. Due to the large sample size, we chose a *P* value <0.01 to represent the threshold of statistical significance.

Descriptive Statistics

Stroke type-specific descriptive characteristics were compared between those with prevalent HF and those without at the baseline (index admission in the database) using the independent-sample t-test, Mann-Whitney U test and Chi-squared test, as appropriate.

Analysis of in-hospital mortality

Logistic regressions were used to examine the impact of HF on in-hospital mortality. We performed analyses for the entire cohort and then stratified by 3 categories (ischemic, haemorrhagic and stroke of undetermined pathology). In order to minimise confounding, we selected covariates according to previous literature [4-8] to be included in the multivariable logistic regression model. All models were adjusted for age, sex, co-morbidities (hypertension, diabetes mellitus, dyslipidaemia, ischaemic heart disease, valvular disease, atrial fibrillation, other arrhythmias, peripheral vascular disease, cancers, chronic obstructive pulmonary disease, liver disease, anaemia, alcohol-related disorders, neurodegenerative disorders) and admission parameters (fever, hypoglycaemia, hyperglycaemia). Additional sensitivity analyses were performed with adjustments limited to age, sex, cancer and important cardiovascular co-morbidities (hypertension, diabetes, hyperlipidaemia, ischaemic heart disease, valvular heart disease, atrial fibrillation, other arrhythmias, and peripheral vascular disease).

Analysis of long-term post-discharge mortality

To examine the influence of HF on long term mortality, we constructed a survival model based on a flexible parametric regression [11], using restricted cubic splines (RCS). The number of internal knots was chosen pragmatically in line with existing literature [12,

13] for our sample size. The proportional hazards (PH) assumption was verified using log negative log plots. The hazard ratios (HR) for the variables which violated the PH assumption were modelled parametrically using the Weibull distribution. When HF was found violate the PH assumption, the HR was modelled using RCSs with 5 internal knots. Models were adjusted for the same confounders as above. Any new HF diagnosis after discharge was included as a binary time-updated variable in the models.

Analysis of long-term post-discharge mortality and recurrence

We constructed 3 transition multi-state models illustrating the typical natural course of a stroke patient (Figure 1). This part of the analysis was confined to first-ever stroke cases, given that one of the outcomes of the multi-state model was stroke recurrence. Furthermore, only stroke cases with an identified stroke type (either AIS or ICH) were included. All models were adjusted for any post-discharge incident HF or any of the adjusting co-morbidities. . Each transition was modelled using the same protocol as above. The simulation method [12] was employed to estimate the transition probabilities and their 99% confidence intervals. Models were adjusted for the same confounders as above. Additional sensitivity analyses with limited adjustments were performed for transitions 1 and 2.

RESULTS

Patient population & Descriptive Statistics

A flowchart of the patient population is illustrated in Figure 2. After applying the exclusion criteria, a total of 608,890 stroke cases were included. There were 370,527 (60.85%) cases of AIS, 173,236 (28.45%) cases of ICH and 65,127 (10.70%) cases of stroke with an undetermined pathology.

The patient characteristics on admission are summarised in Table 1. Patients had a mean age (SD) of 64.3 (13.7). There were 55.1% males. Patients with pre-existing HF (compared to those without) were older, more likely to be female, spend more time in hospital and have a higher co-morbidity burden across all stroke types. The admission parameters, in-hospital complications and procedures are summarised Table 2. Patients with pre-existing HF (compared to those without) were more likely to be hypoglycaemic on admission, die in hospital and suffer complications (respiratory failure, pneumonia, sepsis, shock, myocardial infarction, acute kidney injury, pulmonary oedema) during the hospital stay across all stroke types. Patients with HF who were admitted with AIS were more likely to be comatose in-hospital. Patients with HF and AIS were more likely to receive IV thrombolytic treatment than those without.

	All Strokes		Acute Ischemic Stroke		Intracerebral Hemorrhage		Stroke of undetermined pathology	
	HF (n = 15,397)	No HF (n = 593,493)	HF (n = 11,522)	No HF (n = 359,005)	HF (n = 2464)	No HF (n = 170,772)	HF (n = 1411)	No HF (n = 63,716)
Age	66.97 (13.81)	64.22 (13.71)	67.49 (13.70)	65.47 (13.24)	63.69 (14.08)	61.12 (14.28)	68.46 (1.40)	65.47 (13.41)
Sex M F	 6989 (45.40%) 8408 (54.61%)	 328,328 (55.32%) 265,165 (44.68%)	 5174 (44.91%) 6348 (55.09%)	 192,553 (53.64%) 166,452 (46.36%)	 1204 (48.86%) 1260 (51.14%)	 102,204 (59.85%) 68,568 (40.15%)	 611 (43.30%) 800 (56.70%)	 33,571 (52.69%) 30,145 (47.31%)
Length of Stay	6 (3-12)	3 (2-7)	6 (3-12)	3 (2-6)	7 (3-19)	5 (2-11)	4 (2-8)	3 (2-5)
Co-morbidities at admission								
Hypertension	8398 (54.54%)	289539 (48.79%)	6037 (52.40%)	170207 (47.41%)	1660 (67.37%)	93184 (54.57%)	701 (49.68%)	26148 (41.04%)
Diabetes Mellitus	3565 (23.15%)	100563 (16.94%)	2729 (23.69%)	72705 (20.25%)	538 (21.83%)	16379 (9.59%)	298 (21.12%)	11479 (18.02%)
Dyslipidaemia	3859 (25.06%)	139704 (23.54%)	3180 (27.60%)	112032 (31.21%)	390 (15.83%)	15097 (8.84%)	289 (20.48%)*	12575 (19.74%)*
Ischemic Heart Disease	2400 (15.59%)	16161 (2.72%)	1861 (16.15%)	12196 (3.40%)	289 (11.73%)	2251 (1.32%)	250 (17.72%)	1714 (2.69%)
Valvular Disease	1626 (10.56%)	8746 (1.47%)	1326 (11.51%)	7022 (1.96%)	174 (7.06%)	862 (0.50%)	126 (8.93%)	862 (1.35%)
Atrial Fibrillation	5075 (32.96%)	35173 (5.93%)	4230 (36.71%)	29240 (8.14%)	453 (18.38%)	2973 (1.74%)	392 (27.78%)	2960 (4.65%)
Arrhythmia	421 (2.73%)	4374 (0.74%)	331 (2.87%)	3259 (0.91%)	55 (2.23%)	657 (0.38%)	35 (2.48%)	458 (0.72%)
Peripheral Vascular Disease	108 (0.70%)	1486 (0.25%)	85 (0.74%)	1067 (0.30%)	16 (0.65%)	316 (0.19%)	7 (0.50%)	103 (0.16%)

Cancers	103 (0.67%)*	3136 (0.53%)*	89 (0.77%)*	2094 (0.58%)*	10 (0.41%)*	753 (0.44%)*	4 (0.28%)*	289 (0.45%)*
Chronic Obstructive Pulmonary Disease	756 (4.91%)	10131 (1.71%)	563 (4.89%)	6856 (1.91%)	107 (4.34%)	2126 (1.24%)	86 (6.09%)	1149 (1.80%)
Chronic Kidney Disease	2085 (13.54%)	31173 (5.25%)	1549 (13.44%)	21167 (5.90%)	355 (14.41%)	6850 (4.01%)	181 (12.83%)	3156 (4.95%)
Liver Disease	307 (1.99%)	7302 (1.23%)	222 (1.93%)	3597 (1.00%)	62 (2.52%)*	3149 (1.84%)*	23 (1.63%)	556 (0.87%)
Anaemia	2190 (14.22%)	39809 (6.71%)	1547 (13.43%)	22748 (6.34%)	476 (19.32%)	14071 (8.24%)	167 (11.84%)	2990 (4.69%)
Alcohol-related disorders	92 (0.60%)	7129 (1.20%)	66 (0.57%)	3151 (0.88%)	22 (0.89%)	3485 (2.04%)	4 (0.28%)*	493 (0.77%)*
Neurodegenerative disorders	251 (1.63%)	5811 (0.98%)	213 (1.85%)	4695 (1.31%)	18 (0.73%)	607 (0.36%)	20 (1.42%)*	509 (0.80%)*

Table 1. Patient characteristics and co-morbid conditions at hospital admission. Continuous normally disitributed variables (Age) are presented as mean (SD), whilst continuous non-normal variables (length of stay) are presented as median (inter-quartile range). Categorical variables are presented as frequency (percentage). All between-group differences are statistically significant ($P < 0.01$) unless otherwise specified.

*Between-group difference not statistically significant ($P > 0.01$).

	All Strokes		Acute Ischemic Stroke		Intracerebral Hemorrhage		Stroke of undetermined pathology	
	HF (n = 15,397)	No HF (n = 593,493)	HF (n = 11,522)	No HF (n = 359,005)	HF (n = 2464)	No HF (n = 170,772)	HF (n = 1411)	No HF (n = 63,716)
Admission parameters								
Fever	147 (0.95%)	4214 (0.71%)	102 (0.89%)*	2646 (0.74%)*	27 (1.10%)*	1121 (0.66%)*	18 (1.28%)*	447 (0.70%)*
Hyperglycaemia	231 (1.50%)	7328 (1.23%)	179 (1.55%)*	4936 (1.37%)*	30 (1.22%)*	1834 (1.07%)*	22 (1.56%)*	558 (0.88%)*
Hypoglycaemia	360 (2.34%)	6958 (1.17%)	291 (2.53%)	4683 (1.30%)	39 (1.58%)	1544 (0.90%)	30 (2.13%)	731 (1.15%)
In-hospital complications								
Death	3766 (24.46%)	84645 (14.26%)	2602 (22.58%)	28357 (7.90%)	989 (40.14%)	52850 (30.95%)	175 (12.40%)	3438 (5.40%)
Recurrent stroke	26	1238	17	696	6	378	3	164
Respiratory Failure	3041 (19.75%)	53090 (8.95%)	2305 (20.01%)	21440 (5.97%)	595 (24.15%)	29977 (17.55%)	141 (9.99%)	1673 (2.63%)
Pneumonia	3088 (20.06%)	43936 (7.40%)	2281 (19.80%)	21845 (6.08%)	613 (24.88%)	19620 (11.49%)	194 (13.75%)	2471 (3.88%)
Sepsis	1161 (7.54%)	17061 (2.87%)	881 (7.65%)	9996 (2.78%)	195 (7.91%)	5878 (3.44%)	85 (6.02%)	1187 (1.86%)
Shock	429 (2.79%)	4537 (0.76%)	347 (3.01%)	1964 (0.55%)	57 (2.31%)	2309 (1.35%)	25 (1.77%)	264 (0.41%)
Myocardial Infarction	777 (5.05%)	2139 (0.36%)	619 (5.37%)	1600 (0.45%)	101 (4.10%)	389 (0.23%)	57 (4.04%)	150 (0.24%)
Acute Kidney Injury	1790 (11.63%)	18717 (3.15%)	1408 (12.22%)	12587 (3.51%)	268 (10.88%)	4881 (2.86%)	114 (8.08%)	1249 (1.96%)
Coma	101 (0.66%)	2532 (0.43%)	67 (0.58%)	1194 (0.33%)	23 (0.93%)*	1114 (0.65%)*	11 (0.78%)*	224 (0.35%)*
Pulmonary Oedema	184 (1.20%)	644 (0.11%)	121 (1.05%)	341 (0.09%)	48 (1.95%)	263 (0.15%)	15 (1.06%)	40 (0.06%)
In-hospital procedures								

Mechanical Ventilation	4912 (31.90%)	114710 (19.33%)	3412 (29.61%)	42179 (11.75%)	1274 (51.70%)	68272 (39.98%)	226 (16.02%)	4259 (6.68%)
Tracheostomy	858 (5.57%)	20028 (3.37%)	488 (4.24%)	5364 (1.49%)	336 (13.64%)	14151 (8.29%)	34 (2.41%)	513 (0.81%)
Gastrostomy	3 (0.02%)*	89 (0.01%)*	3 (0.03%)*	44 (0.01%)*	0 (0.00%)*	38 (0.02%)*	0 (0.00%)*	7 (0.01%)*
Thrombolysis	302 (2.62%)	5776 (1.61%)	302 (2.62%)	5776 (1.61%)	NA	NA	NA	NA
Echocardiography	1619 (10.52%)	14217 (2.40%)	1426 (12.38%)	12008 (3.34%)	115 (4.67%)	1427 (0.84%)	78 (5.53%)	782 (1.23%)

Table 2. Admission parameters, in-hospital complications and procedures. All variables are presented as frequency (percentage). All between-group differences are statistically significant ($P < 0.01$) unless otherwise specified.

*Between-group difference not statistically significant ($P > 0.01$).

Analysis of in-hospital mortality

The results of the multivariable logistic regressions with in-hospital death as the outcome are illustrated in Table 3. Pre-existing HF was associated with increased odds of in-hospital death in all 4 models. Overall, there was an increase in odds, whilst the models fitted separately for each stroke type showed the biggest effect in AIS followed by strokes of undetermined pathology and ICH.

	Death in hospital	
	OR [99%CI]	*P* value
All strokes	**1.74[1.65-1.83]**	**< 0.001**
Acute Ischemic Stroke	**2.26[2.12-2.41]**	**< 0.001**
Intracerebral Haemorrhage	**1.39[1.24-1.55]**	**< 0.001**
Stroke of undetermined pathology	**1.75[1.40-2.20]**	**< 0.001**

Table 3. Influence of pre-existing Heart Failure on stroke mortality in hospital (results of multivariable logistic regression with no HF as reference category; adjusted for the co-variates shown in Supplementary Tables 1 & 2.). Results in **bold** are statistically significant ($P < 0.01$).

Analysis of long-term post-discharge mortality

All patients were followed up for a maximum 4108 days for this outcome. Patients with ischaemic, haemorrhagic and undetermined strokes were followed up for a median (95% CI) of 1518 (1511-1525), 1731 (1715-1745) and 2409 (2385-2431) days, respectively. Supplementary Table 2 details the predictors which were included in each model and those that were introduced as time-varying covariates. Co-morbid HF was significantly associated with an excess mortality risk in all the stroke categories, as well as overall. For strokes of undetermined pathology, the HR [99%CI] was 2.01[1.88-2.15], whilst for AIS HR =

1.97[1.92-2.03]. Because the HR was calculated for ICH patients using RCS, the resulting function was not constant with time, and is illustrated in Supplementary Figure 1. This estimate is significant throughout most of the follow-up period. The HR becomes significant on the 13th day post-discharge HR (t=13) = 1.31[1.04-1.64], after which it increases to a maximum at the end of the follow-up period HR (t = 4108) = 2.56[2.03-3.22].

Supplementary Figure 2 and Supplementary Table 3 illustrate the predicted survival functions stratified by HF status and stroke type. Overall, the survival rate is about half for those with HF who survived the index stroke compared to their counterparts without HF.

Analysis of long-term post-discharge mortality and recurrence

For both mortality and recurrence, all patients were followed-up for a maximum of 4108 days. For the mortality outcome, patients with ischaemic and haemorrhagic strokes were followed up for a median (95%CI) of 1583 (1577-1590) and 1802 (1792 – 1814) days, respectively. For the recurrent stroke outcome, patients with ischaemic and haemorrhagic strokes were followed up for a median (95%CI) of 875 (862 – 887) and 778 (767 – 789), respectively. Median follow-up times and 95% confidence intervals were calculated using the reverse Kaplan-Meier method. Supplementary Figure 3 illustrates the first-ever stroke patient population, stratified by stroke type. A total of 302,603 first AIS patients survived to hospital discharge without a recurrent event. Recurrent AIS occurred in 32,036 patients (10.59%). A total of 128,850 (42.58%) patients died during follow-up, 112,073 (37.04%) after their first-ever stroke and 16,777 (5.54%) after their recurrent AIS. We recorded 96,060 first-ever ICH patients who survived to hospital discharge without having experienced stroke recurrence. Recurrent ICH occurred in 7548 (7.86%) patients. A total of 45,335 (47.19%) patients died during follow-up, 40,609 (42.27%) after their first-ever ICH, and 4726 (4.92%) after their recurrent bleed.

Supplementary Table 4 displays the variables included in the models constructed for each transition and those that were introduced as time-updated variables.

Supplementary Figure 4, Supplementary Table 5 and Figure 3 illustrate the predicted recurrence-free survival, recurrence and mortality probabilities stratified by HF status and stroke type. Supplementary Table 6 illustrates the follow-up post-discharge time when the maximum recurrence probability is reached and its value stratified by HF status and stroke type.

Supplementary Table 7 and Figure 4 illustrate the HRs for each transition for each stroke type, calculated for patients with co-morbid HF (with no HF as reference). For AIS patients the HR function for recurrence was not statistically significant throughout the follow-up period. In the AIS cohort, the HR for recurrence-free mortality was 1.69[1.64-1.74]. For post-recurrence death, HR = 1.45[1.34-1.57]. In ICH patients, the HR function for the recurrence outcome was not statistically significant except for the period between the 157th and the 1158th days post-discharge. The maximum value of the HR during this period was HR (t=387) = 1.79[1.18-2.73]. For the recurrence-free mortality outcome, the HR function was not significant for the first 89 days post-discharge. Following this period, the value of the HR function increases constantly to a maximum of HR (t=4108) = 2.59[2.07-3.26] at the end of the period. HF was not associated with post-ICH mortality: HR = 1.28[0.99-1.66].

The results of our sensitivity analyses with limited adjustments yielded similar results (Supplementary Figure 5). HF was not associated with AIS recurrence. The HR for post-AIS death was higher, HR = 2.01 [1.95-2.07]. The association between HF and ICH recurrence was significant between the 31st and 1130th days after discharge, reaching a maximum of HR (t=360) = 1.84[1.22-2.77]. The association between HF and post-ICH death was significant throughout the follow-up period: the HR function starts from a value of HR (t=7) = 1.31[1.03-1.67] immediately after discharge and increases constantly until it reaches a plateau

at around 1.5 years after discharge HR (t=449) = 2.43[2.06-2.86]. The function then increases constantly until the end of the follow-up period HR (t=4108) = 2.98[2.37-3.75].

DISCUSSION

Our findings indicate that HF predicts worse mortality outcomes in-hospital and during the long-term follow-up, both before and after stroke recurrence. However, certain important differences between AIS and ICH patients exist. In ICH, HF was not associated with an increased risk of post-discharge death in the very short follow-up (before ~3 months). After this period, the increased risk of death associated with a HF diagnosis was higher for ICH than AIS patients. Comparing the recurrence-free survival probabilities of ICH patients with and without HF, it becomes apparent that these results may arise from the high mortality of ICH patients in the short-term post-discharge period. Our analysis suggests that HF seems to influence outcomes **only** after ICH patients stabilize and their mortality rate decreases. It has been well recognized that intracranial haemorrhagic events can cause serious cardiac side-effects [14], including cardiac failure. It may thus be that ICH patients with co-morbid HF may be more likely to suffer cardiac decompensation, leading to an increased risk of death.

Our statistical models yielded no association between HF and AIS recurrence. HF was associated with recurrent ICH **only** within the first 18 months. This revealed that there may be a 'window' within the first 30 months post-discharge when HF patients with ICH have an increased risk of both recurrent stroke and death, after which only the mortality risk persists.

It is possible that the observed changes in the significance of ICH recurrence, occurring at around 2.5 years post-discharge, may be attributable to the contribution of more severe stroke types. As the patients with a more severe clinical presentation leave the cohort

(as they die) at ~ 2 years post-discharge, it is likely that this effect diminishes and thus the HR becomes insignificant. Nevertheless, in the absence of an objective measure of stroke severity, our hypothesis cannot be tested. Future work focusing on the impact of HF on stroke outcomes should therefore account for both stroke and HF severity.

The relationship between HF and post-AIS mortality has been previously studied [1, 4-8, 14-20], showing that the co-existent HF increases the mortality risk both in-hospital [5-8, 15] and after discharge [4-8, 16-20].

A previous meta-analysis [1] suggests that there is a two-fold increase in the risk of AIS recurrence associated with co-morbid HF. Nevertheless, our results appear to show that patients with HF were not at a higher risk of recurrent AIS than those without. Whilst this is based on observational data, our results appear to point into a similar direction as the recent COMMANDER HF trial, which showed that rivaroxaban anticoagulation was not associated with a reduction in the rate of stroke in heart failure patients [21].

The data regarding the influence of co-morbid HF on post-ICH mortality is scarce [22]. We have shown that the impact of HF on ICH mortality is substantial, with a two-fold mortality risk increase. Since previous studies on ICH recurrence [23, 24] have only focused on the radiological characteristics of the primary event, we are the first to evaluate the influence of co-morbid HF on ICH recurrence in the long-term.

The mechanisms behind the association between HF and ICH recurrence remain nevertheless unclear. It may simply be that HF patients are more likely to receive anti-thrombotic therapy [2] due to underlying co-morbidities (coronary artery disease, valvular disease and atrial fibrillation), thus rendering these patients more prone to haemorrhagic events [25, 26]. Whilst we were unable to explore this further in the current analysis, our results suggest that caution should be exerted with HF management strategies that may cause

haematological disturbances in patients with ICH. A balanced risk-vs-benefit approach may thus be desirable in the first 18 months after the acute event.

Our study has several strengths. We have utilized a prospectively-identified multi-centre national cohort, thus minimising the potential selection bias. To the best of our knowledge, this is the first study to differentially analyse the relationship between HF and long-term outcomes of AIS and ICH. Our analysis provides granular insight regarding the dynamic nature of the HF-associated increased risk of death and event recurrence. This has so far not been possible in previous studies. By employing multi-state survival methods and modelling the transition probabilities using flexible parametric techniques, we have managed to overcome the limitations of classical survival analysis models [27]. Furthermore, we have also estimated the absolute probabilities of recurrence-free survival, recurrence and death for both AIS and ICH, stratified by the HF status. By updating any post-discharge HF diagnoses in our statistical models, we have more accurately captured the real distribution of this co-morbidity in our population. We have for the first time illustrated the time-varying nature of the excess mortality and recurrence risk associated with co-morbid HF in both stroke types. We are the very first study assessing the relationship between HF and cerebrovascular disease in Asians, population in which stroke epidemiology is markedly different [28, 29].

We acknowledge certain limitations. Having based all of our analyses on insurance data, case ascertainment was performed using ICD10 codes. We thus lack data regarding stroke severity and the clinical characteristics of HF (severity, ejection fraction, aetiology). Given that stroke severity may be an important determinant of post-stroke prognosis, it may be not be possible to confirm a direct relationship between HF and adverse stroke outcomes. Furthermore, our data may not be applicable in other populations and different healthcare systems. It is important to underline that our cohort was significantly younger than Western stroke cohorts [5-8]. Nevertheless, the pathophysiological link between HF and stroke is

unlikely to be significantly different, highlighted by the fact that our results are concordant with previous literature. Our cohort enrolment occurred over 12 years and time-dependent differences may exist in case ascertainment and management. Nevertheless, this remains one of the inherent limitations of long-term follow-up studies. Our data did not include any information regarding post-discharge medications or ancillary procedures and we were thus unable to explore the effect of HF therapy or antithrombotic medication on outcomes. Finally, we were not able to evaluate the causes of death.

In summary, we report for the first time the impact of co-morbid HF on the clinical trajectories of acute stroke patients, providing stroke-type specific prognostic information. We have shown that co-morbid HF significantly increases the risk of in-hospital and post-discharge death in both AIS and ICH, with the effect on ICH patients being more pronounced. Whilst HF was not associated with AIS recurrence, it was associated with ICH recurrence in those surviving beyond 4 months (2 folds increase in RR) within first 30 months. The cautious use of antithrombotic agents may be advised in HF patients with ICH who remain at a high risk of recurrent events within first 30 months of the acute haemorrhagic event.

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PKM and TAP conceived the study, ST & KS obtained the data and ethical approval. TAP reviewed the literature and carried out statistical analysis under supervision of ADW and ABC. TAP drafted the manuscript and all authors contributed to the interpretation of results and in making an important intellectual contribution to the manuscript. PKM is the guarantor.

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FIGURE LEGENDS

Figure 1. Transitions used in creating the multistate models.

Figure 2. Patient population flowchart.

Figure 3. Stacked graphs showing the predicted probabilities of being in each state (recurrence-free survival, recurrence and mortality) stratified for HF status. Separate calculations were performed for each stroke type.

Figure 4. Hazard Ratio (HR) functions plotted against the post-discharge follow-up time. The solid line represents the point estimate, whilst the shaded area is bound by the limits of the 99% confidence interval. The dashed line represents the reference line (HR = 1).

Supplementary Data

Disease classification	ICD 10 code
Acute Ischaemic Stroke	I63; I63.0; I63.1; I63.2; I63.3; I63.4; I63.5; I63.6; I63.8; I63.9
Intracerebral Haemorrhage	I61; I61.0; I61.1; I61.2; I61.3; I61.4; I61.5; I61.6; I61.8; I61.9
Stroke of undetermined pathology	I64
Heart Failure	I25.5; I42.0; I42.9; I50; I50.0; I50.1; I50.9; I51.7
Hypertension	I10; I11.0; I11.9; I12.0; I12.9; I15.1; I15.2; I15.8; I15.9;
Diabetes Mellitus	E10.9; E11.0; E11.2; E11.3; E11.4; E11.5; E11.6; E11.8; E11.9
Dyslipidaemia	E75.6; E78.0; E78.1; E78.2; E78.3; E78.4; E78.5; E78.6; E78.8; E78.9
Ischaemic Heart Disease	I20.0; I20.9; I25.0; I25.1; I25.2; I25.8; I25.9
Valvular Disease	I06.2; I061; I060; I05.2; I05.9; I05.1; I05.0; I07.1; I08.0; I08.1; I08.3; I09.9; I35.1; I35.2; I35.0; I34.2; I34.0; I34.1
Atrial Fibrillation	I48
Arrhythmia	I49.0; I49.1; I49.3; I49.4; I49.5; I49.8; I49.9; R00; R00.0; R00.1; R00.2
Peripheral Vascular Disease	I70.1; I70.2; I70.8; I70.9; I71.0; I71.2; I71.4; I71.9; I72.9; I73.9; I74.2; I74.3; I74.9; I77.1; I77.6
Cancers	C11.9; C18.9; C20; C22.0; C22.1; C34.9; C50.9; C53.9; C61; C67.9; C73; C77.9; C78.2; C79.3; C79.5; C79.8
Chronic Obstructive Pulmonary Disease	J42; J43.9; J44; J44.0
Chronic Kidney Disease	N18; N18.0; N18.1; N18.2; N18.3; N18.4; N18.5; N18.9; N19; Z99.2
Liver Disease	K70.1; K70.3; K71.2; K71.6; K72.0; K72.9; K74.6; K75.0; K75.8; K75.9; K76.0; K76.9; R18
Anaemia	D50.0; D50.8; D50.9; D52.9; D53.1; D53.9; D61.9; D62; D63; D63.0; D63.1; D63.8; D64.8; D64.9
Alcohol-related disorders	F10.0; F10.1; F10.2; F10.20
Neurodegenerative disorders	F03; F03.0; G31.0; G31.1; G31.9
Fever	R50.8; R50.9
Hyperglycaemia	R73.0; R73.9
Hypoglycaemia	E16.1; E16.2
Respiratory Failure	J96; J96.0; J96.1; J96.9
Pneumonia	J13; J14; J15; J15.0; J15.1; J15.2; J15.4; J15.5; J15.6; J15.8; J15.9; J18; J18.0; J18.1; J18.2; J18.8; J18.9; J22
Sepsis	A02.1; A40.1; A40.8; A40.9; A41; A41.0; A41.1; A41.2; A41.5; A41.8; A41.9; B37.7; E02; R65.2
Shock	R57; R57.0; R57.1; R57.8; R57.9
Myocardial Infarction	I21; I21.0I21.4; I21.1; I21.2; I21.3; I22.9; I24.9
Acute Kidney Injury	N10; N17; N17.0; N17.8; N17.9
Coma	E15; R40.2
Pulmonary Oedema	J81
Procedure	**ICD 9 code**
Mechanical Ventilation	9390; 9670; 9671; 9672
Tracheostomy	311; 3129
Gastrostomy	4311
Thrombolysis	9910
Echocardiography	8872

Supplementary Table 1. International Classification of Disease codes utilised in extracting the data regarding the listed co-morbidities, complications and procedures from the insurance database.

	Acute Ischaemic Stroke	Intracerebral Haemorrhage	Stroke of undetermined pathology
Age			
Sex	*		*
Heart Failure		**	
Hypertension	*		*
Diabetes Mellitus	*	*	*
Dyslipidaemia			
Ischaemic Heart Disease			*
Valvular disease			
Atrial Fibrillation			
Arrhythmias		*	*
Peripheral Vascular Disease			
Cancers			
Chronic Obstructive Pulmonary Disease			
Chronic Kidney Disease			
Liver Disease			
Anaemia			
Alcohol-related disorders	*	*	*
Neurodegenerative disorders		*	
Fever		*	
Hyperglycaemia	*		
Hypoglycaemia		*	

Supplementary Table 2. Co-variates included in the multivariable models with the outcome of long-term mortality.*Variable was found to be non-concordant with the proportional hazards assumption and was modelled as a non-constant function of time using the Weibull distribution. ** Variable was found to be non-concordant with the proportional hazards assumption and was modelled as a non-constant function of time using restricted cubic splines with 5 degrees of freedom.

	HF (10 year - Survival [99%CI])	No HF (10 year -Survival [99%CI])
Ischaemic	17.92% [17.24% - 18.63%]	37.28% [36.93% - 37.65%]
Haemorrhagic	18.87% [16.63% - 21.41%]	38.6% [38.07% - 39.08%]
Undetermined	15.72% [14.30% - 17.27%]	34.78% [34.15% - 35.42%]

Supplementary Table 3. Predicted values of the survival functions (presented as point estimates and 99% confidence interval values) for stroke type calculated for patients with and without co-morbid HF.

Stroke Type	Acute Ischaemic Stroke			Intracerebral Haemorrhage		
Transition	Baseline – Recurrent stroke	Baseline-Death	Recurrent stroke - Death	Baseline – Recurrent stroke	Baseline-Death	Recurrent stroke - Death
Age	*			*		*
Sex	*	*	*			
Heart Failure	**			**	**	
Hypertension	*	*	*	*		*
Diabetes Mellitus	*	*	*	*	*	*
Dyslipidaemia				*		*
Ischaemic Heart Disease	*		*	*		
Valvular disease						
Atrial Fibrillation				*		
Arrhythmias			*	*	*	
Peripheral Vascular Disease	*		*	*		*
Cancers	*		*	*		
Chronic Obstructive Pulmonary Disease	*		*	*		*
Chronic Kidney Disease	*			*		
Liver Disease	*		*	*		*
Anaemia	*			*	*	*
Alcohol-related disorders	*		*	*	*	*
Neurodegenerative disorders	*			*	*	*
Fever	*			*	*	*
Hyperglycaemia	*	*		*		*
Hypoglycaemia	*		*	*	*	*

Supplementary Table 4. Co-variates included in the transition multivariable models used to construct the multistate statistical model

*Variable was found to be non-concordant with the proportional hazards assumption and was modelled as a non-constant function of time using the Weibull distribution.

** Variable was found to be non-concordant with the proportional hazards assumption and was modelled as a non-constant function of time using restricted cubic splines with 5 degrees of freedom.

	10-year Recurrence Free Survival		10-year recurrence probability		10-year Mortality probability	
	HF	No HF	HF	No HF	HF	No HF
Ischaemic	15.27%[13.98%-16.47%]	28.21%[27.05%-53.46%]	2.91%[2.41%-3.57%]	4.19%[3.67%-5.70%]	81.72%[80.41%-83.12%]	67.65%[66.24%-43.69%]
Haemorrhagic	12.01%[9.03%-15.26%]	24.73%[23.18%-41.42%]	1.08%[0.58%-1.72%]	2.30%[1.88%-3.16%]	86.88%[83.54%-89.79%]	72.96%[71.34%-59.07%]

Supplementary Table 5. Probability of recurrence-free survival, recurrence and mortality at 10 years and the 99% confidence interval for each stroke type, stratified by HF status.

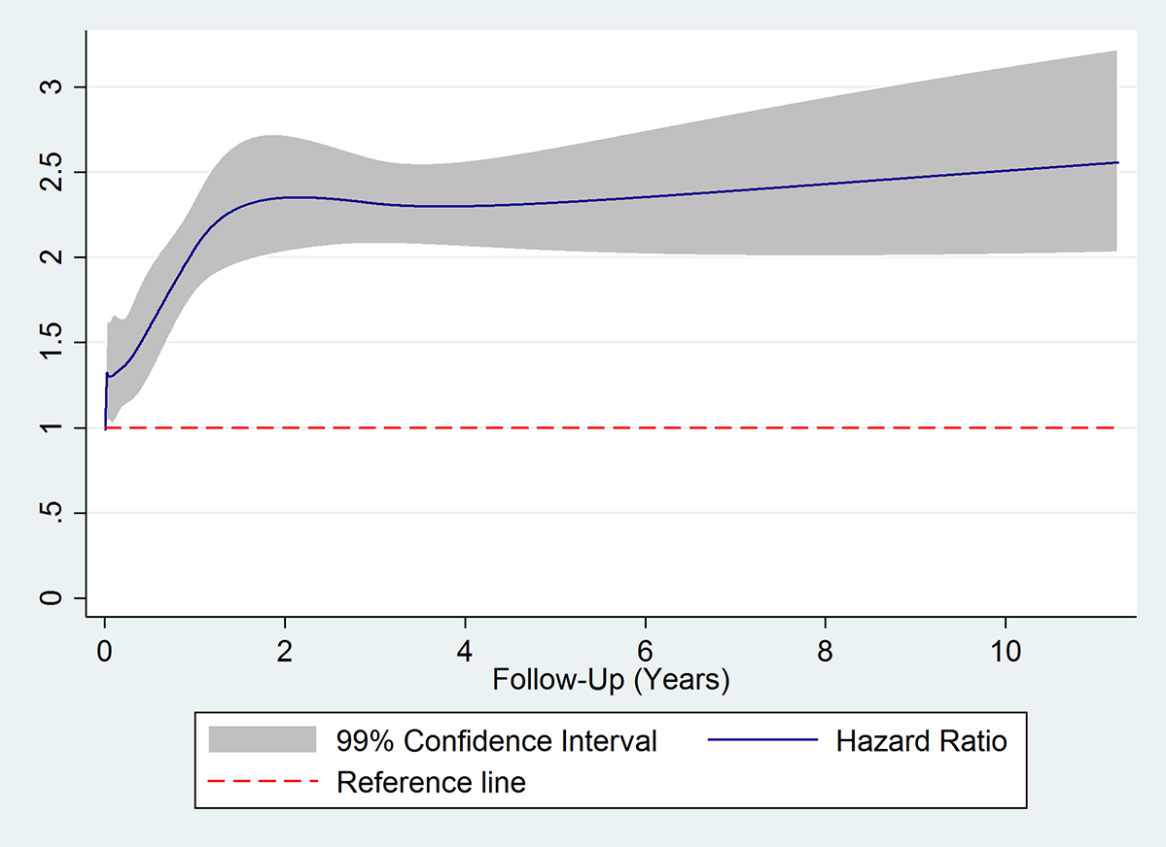
	HF		No HF	
	Follow-Up Time (days)	P [99% CI]	Follow-Up Time (days)	P [99% CI]
Ischaemic	1579	4.46%[3.87%-5.02%]	1747	5.25%[4.72%-5.82%]
Haemorrhagic	404	2.72%[1.90%-3.68%]	45	3.12%[2.60%-3.58%]

Supplementary Table 6. Maximum probability of recurrence for each stroke type and day of follow-up when achieved, stratified by HF status.

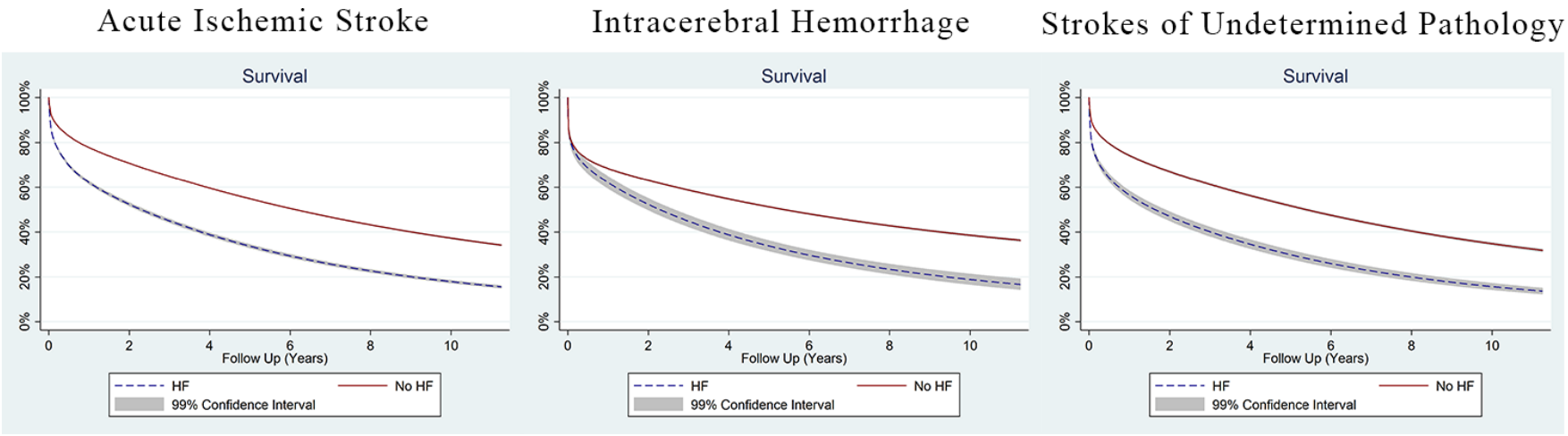
	AIS	ICH
Transition	HR[99% CI]	HR[99% CI]
Baseline – Recurrent stroke	*	*
Baseline – death	1.54 [1.48-1.61]]	*
Recurrent stroke – death	1.27 [1.16-1.40]	1.46 [1.14-1.88]

*Hazard Ratio modelled as a function of time due to non-concordance with the proportional hazard assumption. Graph of the function illustrated in Figure 6

Supplementary Table 7. Hazard Ratios of each transition, calculated for patients with HF (with no HF as reference).

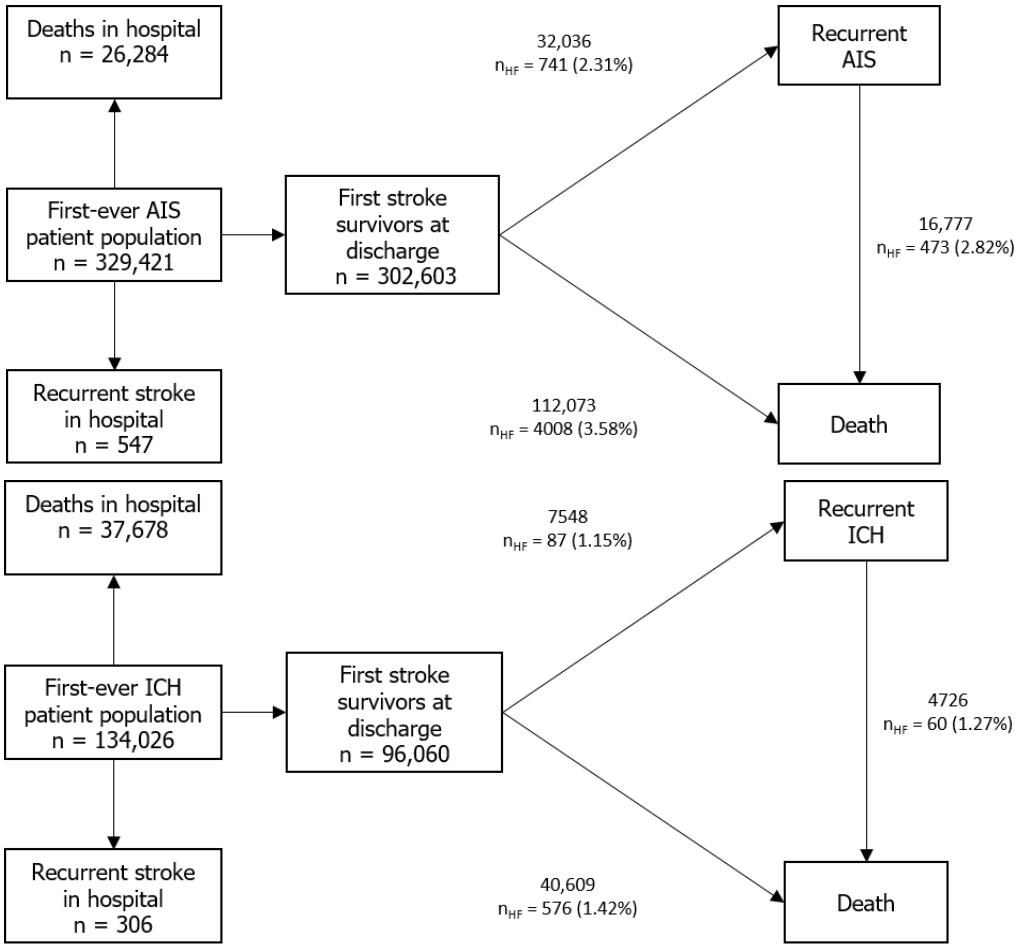


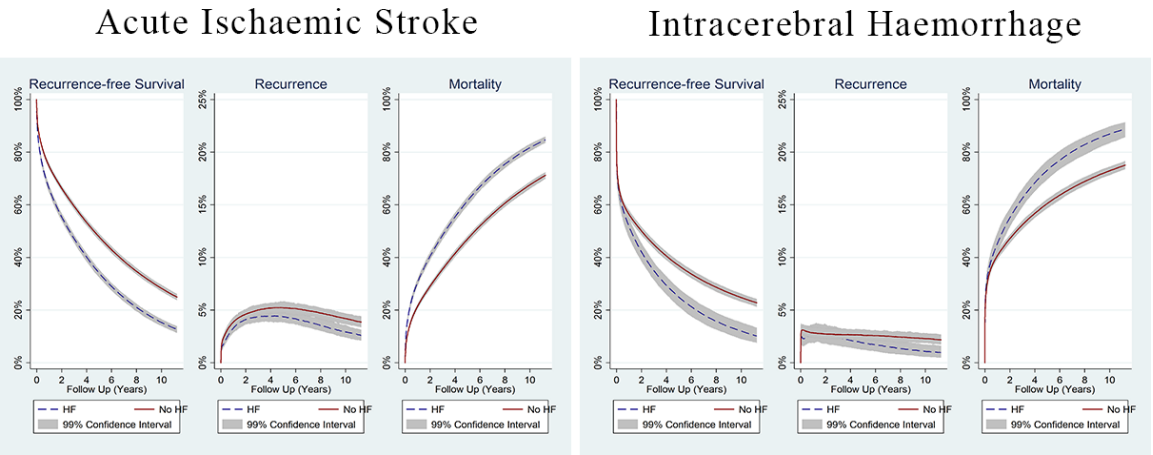
Supplementary Figure 1. The hazard ratio (HR) calculated for patients with intracerebral haemorrhage and co-morbid heart failure (with no heart failure as the reference category). The solid line represents the point estimate, whilst the shaded area is bound by the extreme values of the 99% confidence interval



Supplementary Figure 2. Predicted survival probability stratified by HF status. Separate calculations were performed for each stroke type. The solid line represents the point estimates in patients without co-morbid heart failure, whilst the dashed line represents the point estimates in patients with co-morbid heart failure. The shaded areas are bound by the extreme values of the 99% confidence interval for each respective point estimate

Supplementary Figure 3. Flowchart of first-ever stroke patients admitted with Acute Ischemic Stroke (AIS) and Intracranial Haemorrhage (ICH) respectively.





Supplementary Figure 4. Predicted probabilities of being in each state (recurrence-free survival, recurrence and mortality) stratified for HF status. Separate calculations were performed for each stroke type. The solid line represents the point estimates in patients without co-morbid heart failure, whilst the dashed line represents the point estimates in patients with co-morbid heart failure. The shaded areas are bound by the extreme values of the 99% confidence interval for each respective point estimate.

Supplementary Figure 5. Results of the sensitivity multi-state analysis adjusting only for cardiovascular co-morbidities. Hazard Ratio (HR) functions were plotted against the post-discharge follow-up time. The solid line represents the point estimate, whilst the shaded area is bound by the limits of the 99% confidence interval. The dashed line represents the reference line (HR = 1).