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Hoad, K, Buckley, B, Helen, J, Miller, G, Lip, G and Abdul-Rahim, A Stroke-Heart Syndrome: Incidence and Clinical Outcomes of Cardiac Complications Following Intracerebral Haemorrhage. European Stroke Journal. ISSN 2396-9873 (Accepted)

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Stroke-Heart Syndrome: Incidence and Clinical Outcomes of Cardiac Complications Following Intracerebral Haemorrhage

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Manuscript word count 4343 *(including Title Page, Abstract, Text, References, Tables and Figures)*

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Abstract

Introduction: Newly diagnosed cardiovascular complications following an ischaemic stroke, termed stroke-heart syndrome, are common and associated with worse outcomes. Little is known regarding stroke-heart syndrome in relation to intracerebral haemorrhage (ICH). This study aimed to investigate the incidence and 5-year major adverse cardiovascular events (MACE; acute myocardial infarction, ischaemic stroke, all-cause mortality and recurrent ICH) of newly diagnosed cardiovascular complications following incident ICH, using a global federated database.

Methods: A retrospective cohort study was conducted using anonymised electronic medical records. Patients aged ≥18 years with non-traumatic ICH and 5-year follow-up were included. Patients with newly diagnosed cardiovascular complications *within 4-weeks* following the initial ICH were 1:1 propensity score-matched with patients without new-onset cardiovascular complications. Each cardiovascular complications were investigated as a composite stroke-heart syndrome cohort and separately for

associated MACE. Cox hazard regression models were used to determine 5-year incidence of MACE.

Results: Before propensity score matching, 171,489 patients with non-traumatic ICH, 15% (n = 26,449) experienced ≥1 newly diagnosed cardiovascular complication within 4 weeks. After matching, patients with ICH and cardiovascular complications were associated with a significantly higher risk of 5-year MACE (HR 1.35 [95% CI 1.32-1.38]), and in each composite compared to matched controls. There was no significant risk of rehospitalisation over 5-year follow-up [HR 0.90 [0.73-1.13]). The risk of MACE was significantly higher in patients with newly diagnosed cardiovascular complications.

Conclusions: Newly diagnosed cardiovascular complications following ICH (i.e., stroke-heart syndrome) were common and associated with a significantly worsened 5-year prognosis.

Key Words: stroke-heart syndrome ▪ intracerebral haemorrhage ▪ arrhythmias ▪ heart failure ▪ outcomes

Introduction

Recent studies have demonstrated that newly diagnosed cardiovascular complications following ischaemic stroke are common (approximately 20%) and are associated with a poor prognosis, compared to those without newly diagnosed cardiovascular complications following a stroke[1-3]. The term "stroke-heart syndrome" describes a range of functional, morphological, or biological cardiac changes occurring within the first 30 days following an acute stroke[2, 3]. Clinical manifestations of stroke-heart syndrome include ischaemic heart diseases, heart failure, acute myocardial infarction, atrial and ventricular arrhythmias, and Takotsubo syndrome[2]. These stroke-induced cardiovascular complications may be caused by inflammation, central autonomic dysfunction, and/or myocardial structural changes[4, 5].

Previous research on stroke-heart syndrome has focused on ischaemic stroke[2, 3, 5-7] with little attention given to strokes associated with intracerebral haemorrhage (ICH). Prior ICH cohorts have also generally focused on pre-existing cardiovascular complications, rather than those with incident events following the index ICH presentation. For example, ICH patients with pre-existing cardiovascular complications have an elevated risk of recurrent ICH, ischaemic stroke, and serious vascular events[8]. Pre-existing atrial fibrillation and heart failure in patients with ICH have been shown to increase the risk of ischaemic stroke and mortality[8, 9].

Relatively small studies have investigated new cardiovascular events following ICH. For example, a high percentage of patients with ICH experience new cardiac arrhythmias (including severe ventricular arrhythmias and atrial fibrillation) in the early stages following stroke (8-15%)[10, 11]. In a high proportion (15%) these new ECG abnormalities remain up to 2 weeks following ICH[10]. One retrospective observational

study[11] reported that amongst 1,013 patients with ICH, 4.1% (n = 39) patients experienced in-hospital cardiovascular complications (i.e., severe ventricular arrhythmia, and heart failure). Furthermore, patients with ICH are at an increased risk of in-hospital acute myocardial infarction and mortality[11, 12]. However, no prior research has investigated the long-term implications of these new-onset cardiovascular complications on major adverse cardiovascular events (MACE).

The aim of this study was therefore to investigate the incidence and 5-year major adverse cardiovascular events (MACE) of newly diagnosed cardiovascular complications following incident ICH, using a large global federated database.

Methods

This multicentre retrospective observational cohort study used anonymised electronic medical records (EMRs) from complete case, anonymised data within TriNetX (https://live.trinetx.com), a global federated health research network with access to electronic medical records (EMRs) from participating healthcare organisations (HCOs), including academic medical centres, specialty physician practices, and community hospitals, predominantly in the United States. As no identifiable information is receive in this federated network, research studies using TriNetX do not require ethical approval or patient informed consent.

Study participants

The network was searched on February 8th, 2024, and identified datasets of included data from 2003 to 2023. Patient records were included with at least 5-years of follow-up from index event (i.e., first record of intracerebral haemorrhage (ICH)). This cohort

study adheres to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines[13]. STROBE checklist can be found in Supplemental Material (Table S1). Patients aged ≥18 years with an incident ICH and a minimum of 5-year follow-up were identified from the first instance. Only cases with the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code I61 (non-traumatic intracerebral haemorrhage) were included in the analysis, ensuring exclusion of other types of strokes including traumatic haemorrhage. At the time of the search, 73 participating HCOs were included in the network and provided data. ICH patients who were identified as having a newly diagnosed cardiovascular complication within 4 weeks following an ICH were defined as the exposure (stroke-heart syndrome cohort). They were propensity score-matched in a 1:1 ratio to ICH patients without a new-onset cardiovascular complication (control; ICH only cohort).

Clinical outcomes

Newly diagnosed cardiovascular complications included heart failure (I50), atrial fibrillation/flutter (AF) (I48), Takotsubo syndrome (I51.81), severe ventricular arrhythmia (i.e., ventricular tachycardia (I47.2) and ventricular fibrillation/flutter (I48)), and ischaemic heart diseases (I20-I25) (Table S2). Each of these cardiac complications were investigated as a composite stroke-heart syndrome cohort (primary analysis) and separately (secondary analyses) for associated 5-year MACE. MACE was defined as the presence of any of the following: recurrent ICH, incident ischaemic stroke, all-cause mortality, acute myocardial infarction. The occurrence of MACE was specified as an event subsequent to the diagnosis of ICH up to 5-years follow-up (Table S3).

Statistical analysis

Baseline characteristics were compared using χ2 tests or independent-sample t tests. Using logistic regression, the exposure cohort (i.e., stroke-heart syndrome) were 1:1 propensity score matched to control cohort (i.e., ICH only) for age (at index event), sex, ethnicity, hypertensive diseases, diabetes, cerebrovascular diseases (e.g., transient ischaemic attack and sequelae of cerebrovascular disease), pulmonary heart disease/disease of the pulmonary circulation, cardiovascular procedures (including electrocardiography, echocardiography, catheterization, cardiac devices, and electrophysiological procedures), and cardiovascular medications (including β-blockers, antiarrhythmics, diuretics, antilipemic agents, antianginals, calcium channel blockers, and angiotensin-converting enzyme inhibitors). Comorbidities and cardiovascular care coding are presented in Table S4.

Following propensity score matching, hazard ratios were calculated via Cox hazard regression models with 95% confidence intervals, Kaplan Meier curves and Log Rank p-values were also provided for 5-year incidence of MACE comparing ICH patients with newly diagnosed cardiovascular complications with propensity matched controls (without newly diagnosed post-stroke cardiovascular complications). A two-sided p-value of less than 0.01 was considered statistically significant to account for multiple testing, reducing the likelihood of Type I error. Sensitivity analyses included excluding all patients with pre-existing cardiovascular and respiratory conditions and patients with multiple cardiac complications following ICH.

Results

Clinical characteristics

Before propensity score matching, a total of 171,489 patients (mean age 62.25, SD 19.35; 43.8% female), with ICH were identified from 53 healthcare organisations that met the inclusion criteria with 5-year follow-up (stroke-heart syndrome cohort, n = 26,449; ICH cohort, n = 145,040). Overall, 15% had one or more newly diagnosed cardiovascular complication within 4-weeks of incident ICH 9% (n = 15,413) ischaemic heart disease, 8% (n = 14,175) atrial fibrillation/flutter, 6% (9,980) heart failure, 2% (n = 2,608) severe ventricular arrhythmia, and 0.2% (n = 409) Takotsubo syndrome.

After propensity score matching, there were 8.7% (n = 14,961) patients were identified with ischaemic heart disease, 8.1% (n = 13,855) with atrial fibrillation/flutter, 5.6% (n = 9,622) with heart failure, 1.5% (n = 2,525) with severe ventricular arrhythmia, and 0.2% (n = 409) with Takotsubo syndrome, who were compared to matched controls (ICH without cardiac complications). Overall, cohorts (15%; n = 25,597) were deemed well matched for age, sex, ethnicity, comorbidities and cardiovascular procedures/medications, although pulmonary heart disease and diseases of pulmonary circulation remained statistically different between groups after the propensity score matching (Table 1).

Major Adverse Cardiovascular Events and Cardiovascular Complications

Any cardiovascular complication following ICH were associated with significantly higher risk of composite MACE, compared to matched controls without cardiovascular complications (HR 1.35 [95% CI 1.32-1.38]). When investigating each component of MACE individually, there was significantly higher for acute myocardial infarction (HR

3.64 [95% CI 3.34-3.97]), ischaemic stroke (HR 1.65 [95% CI 1.60-1.71]), all-cause mortality (HR 1.49 [95% CI 1.45-1.53]), and recurrent intracerebral haemorrhage (HR 1.08 [95% CI 1.05-1.11]) in patients with ICH and cardiac complications compared to matched controls (Figure 1). There was no significant risk of rehospitalisation over 5 years follow up (HR 0.90 [95% CI 0.73-1.13]).

When investigating the risk of composite MACE across each cardiovascular complication, there was significantly higher risk for patients with Takotsubo syndrome (HR 1.43 [95% CI 1.21-1.68]), severe ventricular arrhythmia (HR 1.38 [95% CI 1.30-1.47]), heart failure (HR 1.32 [95% CI 1.28-1.37]), ischaemic heart disease (HR 1.30 [95% CI 1.26-1.33]), and atrial fibrillation/flutter (HR 1.28 [95% CI 1.24-1.32]) (Figure 2). In exploratory analysis, multiple cardiovascular complications associated with higher risk of MACE (Figure S1).

Individual Clinical Outcomes

Mortality. The risk of 5-year all-cause mortality was significantly higher for patients with ICH and atrial fibrillation/flutter (HR 1.35 [95% CI 1.30-1.40]), severe ventricular arrhythmia (HR 1.81 [95% CI 1.66-1.97]), heart failure (HR 1.52 [95% CI 1.45-1.59]), and ischaemic heart diseases (HR 1.35 [95% CI 1.30-1.40]) compared to matched controls.

Recurrent ICH. The 5-year risk of recurrent ICH was significantly higher in patients with heart failure when compared to ICH (HR 1.08 [95% CI 1.03-1.13]). There was no significant difference in risk for recurrent ICH with atrial fibrillation/flutter (HR 1.00 [95% CI 0.97-1.04]), or severe ventricular arrhythmia (HR 1.06 [95% CI 0.97-1.15]), when compared to matched controls.

Ischaemic stroke and myocardial infarction. The 5-year risk of ischaemic stroke was significantly higher in all ICH stroke-heart syndrome subgroups: atrial fibrillation/flutter (HR 1.70 [95% CI 1.63-1.78]), heart failure (HR 1.52 [95% CI 1.44-1.60]), severe ventricular arrhythmia (HR 1.44 [95% CI 1.30-1.59]), and ischaemic heart diseases (HR 1.44 [95% CI 1.38-1.51]), compared to matched controls.

The 5-year risk of acute myocardial infarction was significantly higher for patients with ICH and ischaemic heart disease (HR 4.65 [95% CI 4.22-5.13]), heart failure (HR 2.68 [95% CI 2.41-2.98]), severe ventricular arrhythmia (HR 2.64 [95% CI 2.19-3.19]), and atrial fibrillation/flutter (HR 1.72 [95% CI 1.56-1.90]) compared to matched controls. The 5-year risks of acute myocardial infarction had the highest hazard ratio values amongst all MACE outcomes.

Takotsubo syndrome. Following ICH, Takotsubo syndrome was associated with significantly higher risk of composite MACE, compared to matched controls without Takotsubo syndrome (HR 1.43 [95% CI 1.21-1.68]) The separated risks of cardiovascular complications to each composite of 5-year MACE can be found in Figure 3.

Discussion

In this study, our principal findings are as follows: (i) newly diagnosed cardiovascular complications within 4 weeks following an ICH were common (15%; n = 26,449), but this varied across different complications, including ischaemic heart disease (9%; n = 15,413), followed by atrial fibrillation/flutter (8%; 14,175), heart failure (6%; n = 9980), severe ventricular arrhythmia (2%; n = 2,607), and Takotsubo syndrome (0.2%; n = 409); (ii) patients with ICH and a newly diagnosed cardiovascular complication were associated with a greater risk of MACE compared to matched controls, over 5 years follow-up from incident ICH.

In recent studies examining MACE outcomes, patients with incident haemorrhagic and ischaemic strokes and newly diagnosed cardiovascular complication were at a significantly higher risk of MACE[2, 14]. Within 5 years, patients with ICH and newly diagnosed cardiovascular complications were at a greater risk of MACE outcomes compared to those without a cardiovascular complication (HR 1.35 [95% CI 1.32-1.38]). When comparing both ischaemic and haemorrhagic stroke cohorts, an overall similar risk of MACE following cardiac complications can be found. Although patients with haemorrhagic stroke may exhibit higher mortality rates, possibly attributed to the severity of stroke[14]. The risk of MACE culminates within the initial 30 days following ischaemic stroke, likely attributable to stroke-heart syndrome[15]. In this study, the median occurrence was 13 days for the stroke-heart syndrome cohort and 41 days for ICH only cohort (see Figure S2). Although the risk decreases after 30 days, it remains significant within 90 days and persists 1 year following initial stroke[15, 16]. Two smaller studies have reported the incidence of severe ventricular arrhythmia following ICH ranging from 0.3 to 8% within 30 days of an ICH[10, 11]. When compared to an ischaemic stroke-heart syndrome population and patients following transient ischaemic attack

(TIA), the incidence rates of cardiac complications in the current study were largely comparable (2%; n = 2,607)[2, 17].

In the present study, ICH patients with stroke-heart syndrome had a 1.5-fold higher risk of five-year mortality compared to patients with ICH alone. The greatest risk of 5-year mortality was observed among patients with severe ventricular arrhythmias, closely followed by those with heart failure. In a retrospective study using a Taiwanese insurance database of 608,890 stroke patients (28%; n = 173,236 ICH stroke), pre-existing heart failure was associated with an increased risk of post-discharge mortality (OR 2.59 [95% CI 2.07-3.26]) compared to those without pre-existing heart failure[18]. Although the present study specifically focused on cardiac complications following ICH, these findings suggest that patients with ICH and heart failure are associated with a higher risk of mortality, irrespective of whether heart failure develops before or after ICH.

In cases of ischaemic stroke, cardiac arrhythmias or ventricular repolarization changes are the leading cardiac cause of mortality following a stroke[19]. Specifically, patients with ischaemic stroke-heart syndrome had a 2-fold higher risk of five-year mortality, particularly when the cardiac complication was a severe ventricular arrhythmia[4]. The current study shows that ICH patients with newly diagnosed cardiovascular complications had a 4-fold greater risk of 5-year acute myocardial infarction compared to matched controls (ICH without cardiac complications). This is similar to previous work in an ischaemic stroke cohort where those newly diagnosed with ischaemic heart disease were at high risk of a future acute myocardial infarction[2]. Although no known prior work has investigated long-term outcomes of newly diagnosed ischaemic heart disease following ICH, these findings align with previous research on individuals with pre-existing ischaemic heart disease. Specifically, a 3.5% higher risk of acute

myocardial infarction was seen at 10-year follow-up in patients with ICH and pre-existing ischaemic heart disease[18]. Also, Sposato et al.[5] found that stroke patients with subclinical ischaemic heart diseases or a history of acute myocardial infarction were associated with a heightened risk of future acute myocardial infarction due to stroke-induced accelerated coronary artery atherosclerosis, thus highlighting the vulnerability of individuals with ischaemic heart disease to subsequent myocardial infarction.

Heart failure was associated with a significantly higher risk of 5-year recurrent ICH (HR 1.08). Although the reason(s) for this is unclear, this is similar to ICH patients with pre-existing heart failure, who have a 1.8 times higher 3-year risk of recurrent ICH compared to ICH patients without pre-existing heart failure[9]. Potential explanations for this may be decompensation, use of anti-thrombotic treatments, and type of ICH (e.g., lobar ICH which is an independent risk factor for rebleeding)[19, 20]. Indeed, ICH in relation to AF presents even greater uncertainty especially in relation to whether (and when) thromboprophylaxis should be started[21, 22].

Stroke-heart syndrome in patients with ICH did not associate with a higher risk of 5-year rehospitalisation compared to matched controls. It is likely that although rehospitalisation rates did not significantly differ, the cause of rehospitalisation did. It seems probable that for patients with stroke-heart syndrome, rehospitalisation was more likely due to a severe MACE, as denoted by our primary findings, compared to patients with ICH only. Further, rates of rehospitalisation were lower than other MACE outcomes, possibly limiting precision. However, direct measurement of cause of hospitalisation was not possible in this study and therefore warrants future investigation.

The present study highlights the need for a more holistic or integrated care approach to post-stroke management to reduce the cardiovascular risks associated with this high-risk population[23], now advocated by a European Society of Cardiology position paper[24].

Limitations

Information concerning the severity and location of ICH was unavailable. The data available in TriNetX might originate from specific HCO's and regions, potentially introducing biases into the dataset. The cohort examined in the current study spans over 20 years, and it is possible that the time window may include differences in stroke management, health record collection, and the impact of COVID 19 pandemic. Moreover, this study does not include acute cardiac changes of stroke-heart syndrome such as cardiac biomarkers (e.g., high sensitivity troponin or NT-proBNP). Instead, it focuses on newly diagnosed, overt clinical cardiovascular complications, as previously reported[3]. Ultimately, the determination of whether a cardiovascular complication is the result of an ICH event or pre-existed prior to the stroke (potentially exacerbated by ICH) and is subsequently diagnosed due to thorough clinical work up remains uncertain. Prospective observational studies may be able to explore this concept further, such as the Liverpool Heart & Brain Project[25]. Nonetheless, despite these limitations, the clinical importance of the findings remains.

Conclusion

Newly diagnosed cardiovascular complications following ICH (i.e. stroke-heart syndrome) were common and associated with a significantly worsened 5-year

prognosis. Findings underscore the importance of implementing preventive cardiology measures in these patients and the need for further research in this under studied area.

References

1. Kumar S, Selim MH and Caplan LR. Medical complications after stroke. *Lancet Neurol* 2010; 9: 105-118. DOI: 10.1016/S1474-4422(09)70266-2.
2. Buckley BJR, Harrison SL, Hill A, et al. Stroke-Heart Syndrome: Incidence and Clinical Outcomes of Cardiac Complications Following Stroke. *Stroke* 2022; 53: 1759-1763. DOI: 10.1161/STROKEAHA.121.037316.
3. Scheitz JF, Nolte CH, Doehner W, et al. Stroke-heart syndrome: clinical presentation and underlying mechanisms. *Lancet Neurol* 2018; 17: 1109-1120. DOI: 10.1016/S1474-4422(18)30336-3.
4. Nistor IR and Gherasim L. From Neurocardiology to Stroke-Heart Syndrome. *Rom J Intern Med* 2023; 61: 177-185. DOI: 10.2478/rjim-2023-0020.
5. Sposato LA, Hilz MJ, Aspberg S, et al. Post-Stroke Cardiovascular Complications and Neurogenic Cardiac Injury: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2020; 76: 2768-2785. DOI: 10.1016/j.jacc.2020.10.009.
6. Prosser J, MacGregor L, Lees KR, et al. Predictors of early cardiac morbidity and mortality after ischemic stroke. *Stroke* 2007; 38: 2295-2302. DOI: 10.1161/STROKEAHA.106.471813.
7. Lettow I JM, Schlemm E, Boutitie F, Quandt F, Cheng B, Ebinger M, Endres M, Fiebach JB, Thijs V and Lemmens R. Serious adverse events and their impact on functional outcome in acute ischemic stroke in the WAKE-UP trial. *Stroke* 2021; 52: 3768–3776.
8. Li L, Poon MTC, Samarasekera NE, et al. Risks of recurrent stroke and all serious vascular events after spontaneous intracerebral haemorrhage: pooled analyses of two population-based studies. *Lancet Neurol* 2021; 20: 437-447. DOI: 10.1016/S1474-4422(21)00075-2.
9. Pana TA, Wood AD, Perdomo-Lampignano JA, et al. Impact of heart failure on stroke mortality and recurrence. *Heart Asia* 2019; 11: e011139. DOI: 10.1136/heartasia-2018-011139.
10. Daniele O, Caravaglios G, Fierro B, et al. Stroke and cardiac arrhythmias. *J Stroke Cerebrovasc Dis* 2002; 11: 28-33. DOI: 10.1053/jscd.2002.123972.
11. Putaala J, Lehto M, Meretoja A, et al. In-hospital cardiac complications after intracerebral hemorrhage. *Int J Stroke* 2014; 9: 741-746. DOI: 10.1111/ijs.12180.
12. Micheli S, Agnelli G, Caso V, et al. Acute myocardial infarction and heart failure in acute stroke patients: frequency and influence on clinical outcome. *J Neurol* 2012; 259: 106-110. DOI: 10.1007/s00415-011-6136-4.
13. von Elm E AD, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP and Initiative. S. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008; 61: 344-349.
14. Akyea RK, Georgiopoulos G, Iyen B, et al. Comparison of Risk of Serious Cardiovascular Events after Hemorrhagic versus Ischemic Stroke: A Population-Based Study. *Thromb Haemost* 2022; 122: 1921-1931. DOI: 10.1055/a-1873-9092.
15. Sposato LA, Lam M, Allen B, et al. First-Ever Ischemic Stroke and Incident Major Adverse Cardiovascular Events in 93 627 Older Women and Men. *Stroke* 2020; 51: 387-394. DOI: 10.1161/STROKEAHA.119.028066.
16. Carlsson A, Irewall AL, Graipe A, et al. Long-term risk of major adverse cardiovascular events following ischemic stroke or TIA. *Sci Rep* 2023; 13: 8333. DOI: 10.1038/s41598-023-35601-x.
17. Lip GY, Genaidy A, Estes C, et al. Transient ischemic attack events and incident cardiovascular and non-cardiovascular complications: Observations from a large diversified multimorbid cohort. *Eur Stroke J* 2023; 8: 334-343. DOI: 10.1177/23969873221146044.
18. Otite FO, Khandelwal P, Malik AM, et al. Ten-Year Temporal Trends in Medical Complications After Acute Intracerebral Hemorrhage in the United States. *Stroke* 2017; 48: 596-603. DOI: 10.1161/STROKEAHA.116.015746.
19. Yamamoto H, & Bogousslavsky, J. . Mechanisms of second and further strokes. *Journal of Neurology, Neurosurgery & Psychiatry* 1998; 64: 771-776. DOI: 10.1136/jnnp.64.6.771.

20. Passero S, Burgalassi L, D'Andrea P, et al. Recurrence of bleeding in patients with primary intracerebral hemorrhage. *Stroke* 1995; 26: 1189-1192. DOI: 10.1161/01.str.26.7.1189.
21. Chang PY, Wang WT, Wu WL, et al. Oral Anticoagulation Timing in Patients with Acute Ischemic Stroke and Atrial Fibrillation. *Thromb Haemost* 2022; 122: 939-950. DOI: 10.1055/a-1669-4987.
22. Ivany E, Lotto RR, Lip GYH, et al. Managing Uncertainty: Physicians' Decision Making for Stroke Prevention for Patients with Atrial Fibrillation and Intracerebral Hemorrhage. *Thromb Haemost* 2022; 122: 1603-1611. DOI: 10.1055/a-1789-4824.
23. Lip GYH NG. "Novel Clinical Concepts in Thrombosis": Integrated Care for Stroke Management-Easy as ABC. *Thromb Haemost* 2022; 122: 316-319. DOI: 10.1055/a-1632-1777.
24. Lip GYH, Lane DA, Lenarczyk R, et al. Integrated care for optimizing the management of stroke and associated heart disease: a position paper of the European Society of Cardiology Council on Stroke. *Eur Heart J* 2022; 43: 2442-2460. DOI: 10.1093/eurheartj/ehac245.
25. Harrison SL LD, Buckley BJR, Chatterjee K, Alobaida M, Shipley E, Lip GYH. The Liverpool Heart And bRain Project (L-HARP): Protocol for an Observational Cohort Study of Cardiovascular Risk and Outcomes Following Stroke. *Vasc Health Risk Manag* 2022; 18: 313-318. DOI: 10.2147/VHRM.S357829.

Declarations of conflicting interests

BB has received research funding from BMS/Pfizer. GYHL is a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Anthos. No fees are received personally. He is a National Institute for Health and Care Research (NIHR) Senior Investigator and co-PI of the AFFIRMO project on multimorbidity in AF (grant agreement No 899871), TARGET project on digital twins for personalised management of atrial fibrillation and stroke (grant agreement No 101136244) and ARISTOTELES project on artificial intelligence for management of chronic long term conditions (grant agreement No 101080189), which are all funded by the EU's Horizon Europe Research & Innovation programme.

Funding

No specific funding to declare. TriNetX funded the data acquisition.

Informed consent/ethical approval

The data gathered was not subject to requirement of informed consent and ethical approval.

Guarantor statement

Benjamin Buckley

Author contributions

KLH was involved in conception and design of the study, data acquisition, statistical analysis and interpretation of data, drafting and critical revision of the manuscript. BJRB was involved in the conception and design of the study and critical revision of the manuscript. HJ, GM, AHAR and GYHL were involved in the interpretation of data and critical revision of manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Data availability statement

The data that support the findings of this study are available from the TriNetX Analytics Network. https://trinetx.com.

Supplemental material

Supplemental material for this article is available online.

Figures

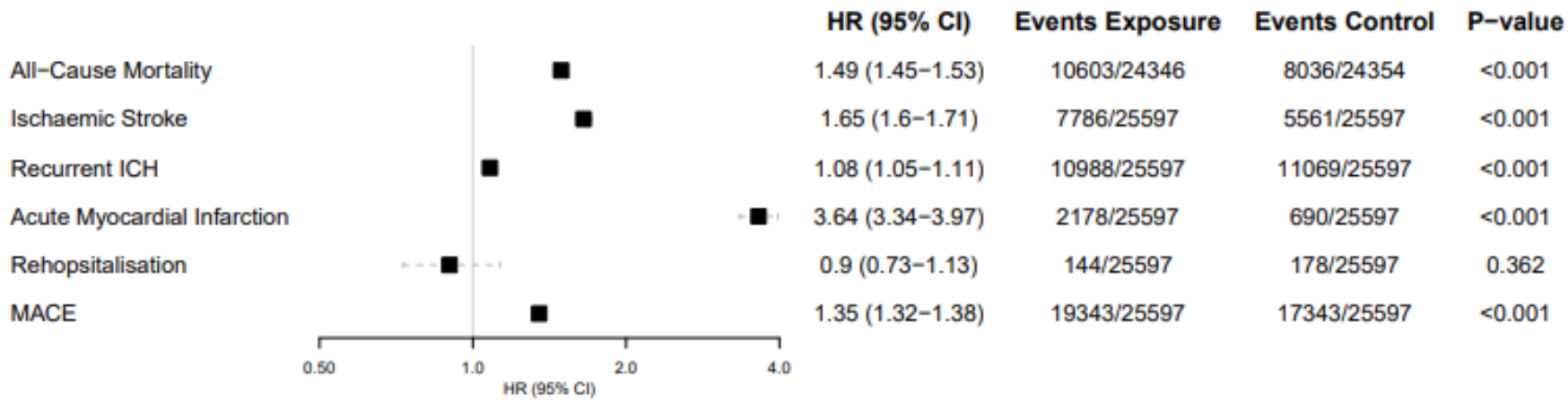

Figure 1. Hazard ratios and 95% confidence intervals for the risk of major adverse cardiovascular events over 5-year follow-up in patients with newly diagnosed cardiovascular complications versus those who were not newly diagnosed with a cardiovascular complications 4-weeks post intracerebral haemorrhagic stroke.

CI, confidence interval; ICH, intracerebral haemorrhage; MACE, major adverse cardiovascular events.

Hazard ratio (HR), through Cox regression models, reported for propensity-score matched cohort.

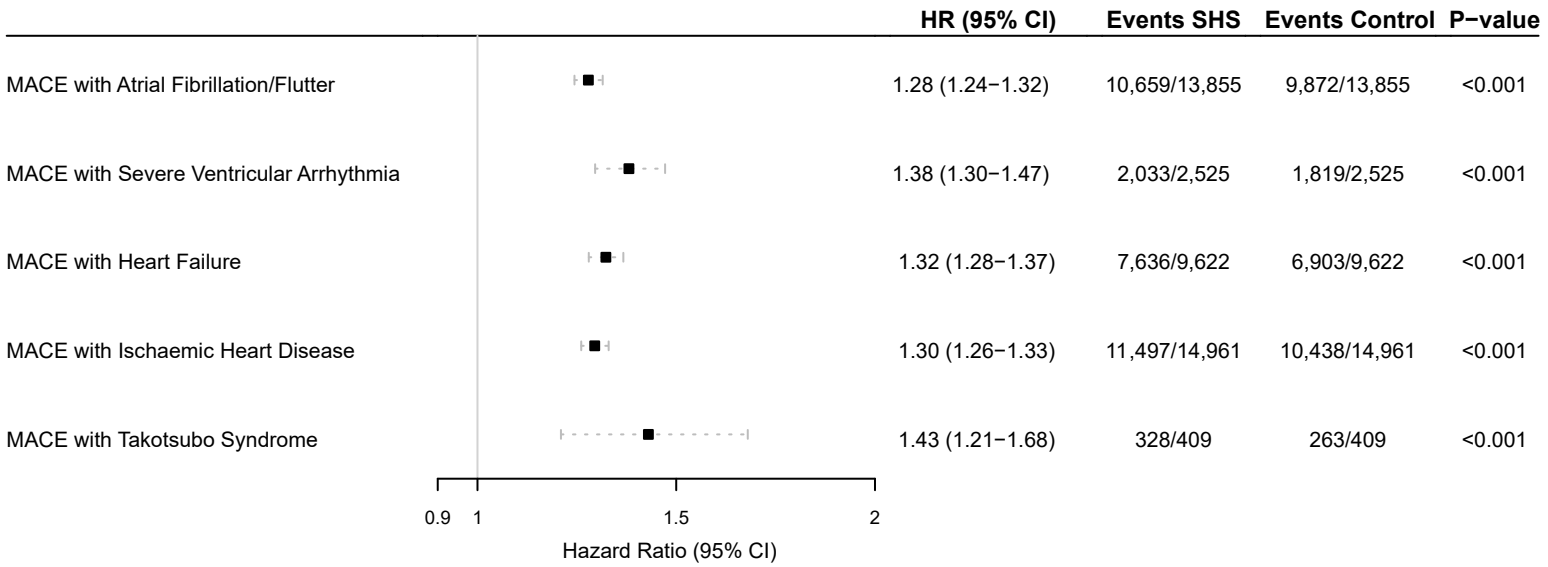

Figure 2. Hazard ratios and 95% confidence intervals for the risk of major adverse cardiovascular events over 5-year follow-up in patients with either atrial fibrillation/flutter, severe ventricular arrhythmias, heart failure, or ischaemic heart diseases versus those who did not have newly diagnosed cardiovascular complications 4-weeks post intracerebral haemorrhagic stroke.

CI, confidence interval; ICH, intracerebral haemorrhage; MACE, major adverse cardiovascular events.

Hazard ratio (HR), through Cox regression models, reported for propensity-score matched cohort.

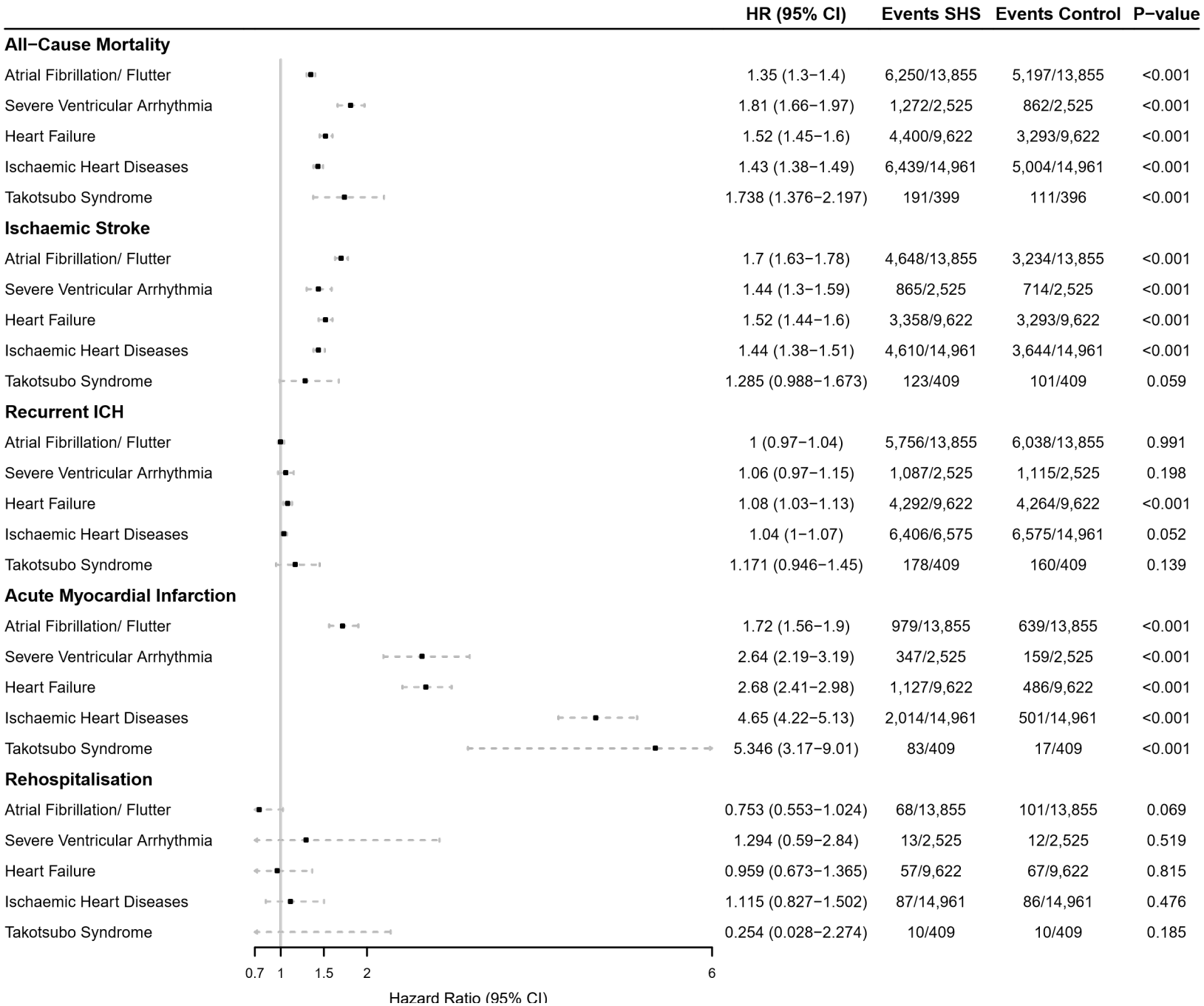
HR (95% CI)
Events SHS
Events Control
P−value
All−Cause Mortality
Atrial Fibrillation/ Flutter 1.35 (1.3−1.4) 6,250/13,855 5,197/13,855 <0.001
Severe Ventricular Arrhythmia 1.81 (1.66−1.97) 1,272/2,525 862/2,525 <0.001
Heart Failure 1.52 (1.45−1.6) 4,400/9,622 3,293/9,622 <0.001
Ischaemic Heart Diseases 1.43 (1.38−1.49) 6,439/14,961 5,004/14,961 <0.001
Takotsubo Syndrome 1.738 (1.376−2.197) 191/399 111/396 <0.001
Ischaemic Stroke
Atrial Fibrillation/ Flutter 1.7 (1.63−1.78) 4,648/13,855 3,234/13,855 <0.001
Severe Ventricular Arrhythmia 1.44 (1.3−1.59) 865/2,525 714/2,525 <0.001
Heart Failure 1.52 (1.44−1.6) 3,358/9,622 3,293/9,622 <0.001
Ischaemic Heart Diseases 1.44 (1.38−1.51) 4,610/14,961 3,644/14,961 <0.001
Takotsubo Syndrome 1.285 (0.988−1.673) 123/409 101/409 0.059
Recurrent ICH
Atrial Fibrillation/ Flutter 1 (0.97−1.04) 5,756/13,855 6,038/13,855 0.991
Severe Ventricular Arrhythmia 1.06 (0.97−1.15) 1,087/2,525 1,115/2,525 0.198
Heart Failure 1.08 (1.03−1.13) 4,292/9,622 4,264/9,622 <0.001
Ischaemic Heart Diseases 1.04 (1−1.07) 6,406/6,575 6,575/14,961 0.052
Takotsubo Syndrome 1.171 (0.946−1.45) 178/409 160/409 0.139
Acute Myocardial Infarction
Atrial Fibrillation/ Flutter 1.72 (1.56−1.9) 979/13,855 639/13,855 <0.001
Severe Ventricular Arrhythmia 2.64 (2.19−3.19) 347/2,525 159/2,525 <0.001
Heart Failure 2.68 (2.41−2.98) 1,127/9,622 486/9,622 <0.001
Ischaemic Heart Diseases 4.65 (4.22−5.13) 2,014/14,961 501/14,961 <0.001
Takotsubo Syndrome 5.346 (3.17−9.01) 83/409 17/409 <0.001
Rehospitalisation
Atrial Fibrillation/ Flutter 0.753 (0.553−1.024) 68/13,855 101/13,855 0.069
Severe Ventricular Arrhythmia 1.294 (0.59−2.84) 13/2,525 12/2,525 0.519
Heart Failure 0.959 (0.673−1.365) 57/9,622 67/9,622 0.815
Ischaemic Heart Diseases 1.115 (0.827−1.502) 87/14,961 86/14,961 0.476
Takotsubo Syndrome 0.254 (0.028−2.274) 10/409 10/409 0.185
0.7
1
1.5
2
6
Hazard Ratio (95% CI)

Figure 3. Hazard ratios and 95% confidence intervals for the risk of each major adverse cardiovascular events composites (all-cause mortality, ischaemic stroke, recurrent intracerebral haemorrhage, acute myocardial infarction, rehospitalisation) over 5-year follow-up in patients with either atrial fibrillation/flutter, severe ventricular arrhythmias, heart failure, or ischaemic heart diseases versus those who did not have newly diagnosed cardiovascular complications 4-weeks post intracerebral haemorrhagic stroke.

CI, confidence interval; ICH, intracerebral haemorrhage; MACE, major adverse cardiovascular events.

Hazard ratio (HR), through Cox regression models, reported for propensity-score matched cohort.

Tables

Table 1. Baseline characteristics n (%) of intracerebral haemorrhagic stroke patients with or without cardiovascular complication(s) (i.e., ischaemic heart disease, heart failure, atrial fibrillation/flutter, Takotsubo syndrome and severe ventricular arrhythmia), before and after propensity score matching.

	Before Propensity-Score Matched Population			After Propensity-Score Matched Population		
	Stroke-heart syndrome cohort (*n* = 26,449)	ICH cohort (*n* = 145,040)	*p* value	Stroke-heart syndrome cohort (*n* = 25,597)	ICH cohort (*n* = 25,597)	*p* value
Age (yrs) at diagnosis Mean (SD)	68.3 (5.4)	56.2 (23.2)	<0.001	68.3 (15.4)	68.4 (15.6)	0.762
Sex						
Male	13,979 (54.6)	71,642 (52.9)	<0.001	13,968 (54.6)	13,931 (54.4)	0.743
Female	10,815 (42.2)	61,357 (45.3)	<0.001	10,815 (42.3)	10,899 (42.6)	0.453
Ethnicity						
White	16,716 (65.3)	82,225 (60.7)	<0.001	16,705 (65.3)	16,776 (65.5)	0.509
Black or African American	3,079 (12.0)	18,659 (13.8)	<0.001	3,079 (12.0)	3,059 (12.0)	0.786
Asian	969 (3.8)	6,191 (4.6)	<0.001	968 (3.8)	980 (3.8)	0.782
Unknown	822 (3.2)	4,366 (3.2)	0.908	822 (3.2)	835 (3.3)	0.745
Comorbidities						
Hypertensive Diseases	5,404 (21.1)	46,635 (34.4)	<0.001	5,404 (21.1)	5,439 (21.2)	0.705
Diabetes Mellitus	2,063 (8.1)	19,268 (14.2)	<0.001	2,062 (8.1)	2,016 (7.9)	0.453
Cerebrovascular Diseases	5,858 (22.9)	36,082 (26.6)	<0.001	5,852 (22.9)	5,783 (22.6)	0.467
Chronic Kidney Disease	963 (3.8)	10,599 (7.8)	<0.001	963 (3.8)	888 (3.5)	0.076
Pulmonary Heart Disease and Diseases of Pulmonary Circulation	476 (1.9)	6,863 (5.1)	<0.001	476 (1.9)	393 (1.5)	0.005
Cardiovascular Care						
Procedures	4,645 (18.1)	42,094 (31.1)	<0.001	4,645 (18.1)	4,642 (18.1)	0.973
Medications	7,135 (27.9)	58,251 (43.0)	<0.001	7,135 (27.9)	7,249 (28.3)	0.262

ICH, intracerebral haemorrhage; SD, standard deviation; yrs, years. $p < 0.01$.

Supplementary Material

Table S1. Strengthening the reporting of observational studies in epidemiology (STROBE) statement. Cohort studies' checklist of included items in report.

	Item Number	Recommendations	Page/section information can be found
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Page 2; abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2-3; abstract
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4-5; introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5; end of introduction
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5-6; methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5-6; methods
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 5-6; methods
		(b) For matched studies, give matching criteria and number of exposed and unexposed	Page 6; methods
Variable	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6; methods
Data sources/ measurements	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6; methods
Bias	9	Describe any efforts to address potential sources of bias	N/a
Study size	10	Explain how the study size was arrived at	N/a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 5+6; methods
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Page 7; methods
		(b) Describe any methods used to examine subgroups and interactions	N/a
		(c) Explain how missing data were addressed	N/a
		(d) If applicable, explain how loss to follow-up was addressed	N/a
		(e) Describe any sensitivity analyses	Page 7; methods
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 8; results
		(b) Give reasons for non-participation at each stage	N/a
		(c) Consider use of a flow diagram	N/a
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential	Page 8; results + Table 1 + Table S1
		(b) Indicate number of participants with missing data for each variable of interest	N/a
		(c) Summarise follow-up time (e.g., average and total amount)	Page Figure S2
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 8-10; results + Figure 1-3
Main results	16	a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 8-10; results + Table 1
		(b) Report category boundaries when continuous variables were categorized	N/a
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 8-10; results

Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	Figure S1
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 14; limitations
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 14; conclusions
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 14; conclusions
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Disclosures

*Give information separately for exposed and unexposed groups in cohort studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Table S2. International Classification of Diseases 10th Revision (ICD-10-CM) codes for cardiovascular complications diagnosed 4-weeks following an intracerebral haemorrhagic stroke.

Cardiovascular complication of stroke-heart syndrome	ICD-10-CM codes
Heart failure	I50
Ventricular tachycardia	I47.2
Ventricular fibrillation and flutter	I49.0
Takotsubo syndrome	I51.81
Ischaemic heart diseases	I20-I25
Unstable angina	I20
Acute myocardial infarction	I21
Subsequent ST elevation and non-ST elevation myocardial infarction	I22
Certain current complications following ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	I23
Other acute ischaemic heart diseases	I24
Chronic ischaemic heart diseases	I25
Atrial fibrillation and flutter	I48

Table S3. International Classification of Diseases 10th Revision codes for 5-year major cardiovascular adverse events.

Cardiovascular complication of stroke-heart syndrome	**ICD-10-CM codes (label)**
Recurrent intracerebral haemorrhage	I61 (nontraumatic intracerebral haemorrhage)

Ischaemic stroke	I63 (cerebral infarction)
All-cause mortality	Deceased
Acute myocardial infarction	I21 (acute myocardial infarction)
Hospitalisation	[SNOMED] 32485007 (hospital admission)

ICD-10-CM, International Classification of Diseases 10th Revision; MACE, major cardiovascular adverse events; SNOMED, systematized nomenclature of medicine clinical terms

Table S4. Baseline characteristics (including pre-stroke comorbidities and cardiovascular care) and coding.

Baseline characteristic	**Code**
Hypertension	I10-I16
Cerebrovascular disease	I60-I69
Diabetes	E08-E13
Pulmonary disease/disease of the pulmonary circulation	I26-I28
Chronic kidney disease	N18
Cardiovascular care	Procedures (CPT 1012974)
	Medications (VA CV000)

Table S5. Baseline characteristics n (%) of intracerebral haemorrhagic stroke patients with or without atrial fibrillation/flutter before and after propensity score matching.

		Before Propensity-Score Matched Population			After Propensity-Score Matched Population		
		Stroke-heart syndrome cohort (*n = 14,175*)	ICH cohort (*n = 162,216*)	*p* value	Stroke-heart syndrome cohort (*n = 13,855*)	ICH cohort (*n = 13,855*)	*p* value
Age (yrs) at diagnosis Mean (SD)		72.9 (2.7)	57.2 (22.7)	<0.001	72.9 (12.7)	72.9 (12.8)	0.855
Sex							
	Male	7,434 (53.7)	80,868 (53.2)	0.330	7,434 (53.7)	7,414 (53.5)	0.810
	Female	5,907 (42.6)	68.151 (44.9)	<0.001	5,907 (42.6)	5,947 (42.9)	0.627
Ethnicity							
	White	9,601 (69.3)	92,386 (60.8)	<0.001	9,600 (69.3)	9,653 (69.7)	0.489
	Black or African American	1,188 (8.6)	21,144 (13.9)	<0.001	1,188 (8.6)	1,184 (8.6)	0.898
	Asian	574 (4.1)	6,776 (4.5)	0.083	574 (4.1)	549 (4.0)	0.446
	Unknown	368 (2.7)	368 (3.2)	<0.001	368 (2.7)	363 (2.6)	0.851
Comorbidities							
	Hypertensive Diseases	3,421 (24.7)	51,538 (33.9)	<0.001	3,421 (24.7)	3,433 (24.8)	0.867
	Diabetes Mellitus	1,440 (10.4)	21,470 (14.1)	<0.001	1,440 (10.4)	1,397 (10.1)	0.394
	Cerebrovascular Diseases	3,183 (23.0)	38,992 (25.7)	<0.001	3,182 (23.0)	3,123 (22.5)	0.398
	Chronic Kidney Disease	756 (5.5)	11,824 (7.8)	<0.001	756 (5.5)	718 (5.2)	0.309
	Pulmonary Heart Disease and Diseases of Pulmonary Circulation	444 (3.2)	7,548 (5.0)	<0.001	444 (3.2)	379 (2.7)	0.021
Cardiovascular Care							
	Procedures	2,912 (21.0)	46,277 (30.5)	<0.001	2,912 (21.0)	2,910 (21.0)	0.976
	Medications	4,233 (30.5)	63,996 (42.1)	<0.001	4,233 (30.6)	4,260 (30.7)	0.725

ICH, intracerebral haemorrhage; SD, standard deviation; yrs, years. $p < 0.01$

Table S6. Baseline characteristics n (%) of intracerebral haemorrhagic stroke patients with or without severe ventricular arrhythmia before and after propensity score matching.

		Before Propensity-Score Matched Population			After Propensity-Score Matched Population		
		Stroke-heart syndrome cohort (*n = 2,608*)	ICH cohort (*n = 173,734*)	*p* value	Stroke-heart syndrome cohort (*n = 2,525*)	ICH cohort (*n = 2,525*)	*p* value
Age (yrs) at diagnosis Mean (SD)		64.2 (17.3)	58.4 (22.6)	<0.001	64.2 (17.3)	64.7 (17.0)	0.296
Sex							
	Male	1,504 (59.6)	86,765 (53.2)	<0.001	1,504 (59.6)	1,516 (60.0)	0.731
	Female	921 (36.5)	73,122 (44.8)	<0.001	921 (36.5)	915 (36.2)	0.861
Ethnicity							
	White	1,500 (59.4)	100,453 (61.5)	0.029	1,500 (59.4)	1,515 (60.0)	0.667
	Black or African American	409 (16.2)	21,916 (13.4)	<0.001	409 (16.2)	418 (16.6)	0.732
	Asian	88 (3.5)	7,262 (4.4)	0.020	88 (3.5)	88 (3.5)	1.000
	Unknown	70 (2.8)	5,192 (3.2)	0.245	70 (2.8)	71 (2.8)	0.932
Comorbidities							
	Hypertensive Diseases	1,100 (43.6)	53,471 (32.8)	<0.001	1,100 (43.6)	1,091 (43.2)	0.798
	Diabetes Mellitus	493 (19.5)	22,319 (13.7)	<0.001	493 (19.5)	503 (19.9)	0.724
	Cerebrovascular Diseases	873 (34.6)	40,164 (24.6)	<0.001	873 (34.6)	875 (34.7)	0.953
	Chronic Kidney Disease	293 (11.6)	12,225 (7.5)	<0.001	293 (11.6)	285 (11.3)	0.724
	Pulmonary Heart Disease and Diseases of Pulmonary Circulation	239 (9.5)	7,690 (4.7)	<0.001	239 (9.5)	200 (7.9)	0.051
Cardiovascular Care							
	Procedures	1,009 (40.0)	47,787 (29.3)	<0.001	1,009 (40.0)	1,005 (39.8)	0.908
	Medications	1,238 (49.0)	66,508 (40.7)	<0.001	1,238 (49.0)	1,222 (48.4)	0.652

ICH, intracerebral haemorrhage; SD, standard deviation; yrs, years. $p < 0.01$

Table S7. Baseline characteristics n (%) of intracerebral haemorrhagic stroke patients with or without heart failure before and after propensity score matching.

		Before Propensity-Score Matched Population			After Propensity-Score Matched Population		
		Stroke-heart syndrome cohort (*n = 9,980*)	ICH cohort (*n = 166,411*)	*p* value	Stroke-heart syndrome cohort (*n = 9,622*)	ICH cohort (*n = 9,622*)	*p* value
Age (yrs) at diagnosis Mean (SD)		67.0 (16.8)	58.0 (22.7)	<0.001	67.0 (16.8)	67.0 (16.8)	0.698
Sex							
	Male	5,175 (53.8)	83,127 (53.2)	0.290	5,175 (53.8)	5,219 (54.2)	0.525
	Female	4,106 (42.7)	69,954 (44.8)	<0.001	4,106 (42.7)	4,101 (42.6)	0.942
Ethnicity							
	White	5,891 (61.2)	96,097 (61.5)	0.544	5,891 (61.2)	5,923 (61.6)	0.636
	Black or African American	1,396 (14.5)	20,936 (13.4)	0.002	1,396 (14.5)	1,424 (14.8)	0.568
	Asian	345 (3.6)	7,005 (4.5)	<0.001	345 (3.6)	346 (3.6)	0.969
	Unknown	277 (2.9)	4,988 (3.2)	0.087	277 (2.9)	278 (2.9)	0.966
Comorbidities							
	Hypertensive Diseases	3,537 (36.8)	51,716 (33.1)	<0.001	3,537 (36.8)	3,544 (36.8)	0.917
	Diabetes Mellitus	1,575 (16.4)	21,468 (13.7)	<0.001	1,575 (16.4)	1,538 (16.0)	0.481
	Cerebrovascular Diseases	3,306 (34.4)	39,106 (25.0)	<0.001	3,306 (34.4)	3,248 (33.8)	0.386
	Chronic Kidney Disease	828 (8.6)	11,845 (7.6)	<0.001	828 (8.6)	786 (8.2)	0.275
	Pulmonary Heart Disease and Diseases of Pulmonary Circulation	460 (4.8)	7,587 (4.9)	0.731	460 (4.8)	377 (3.9)	0.003
Cardiovascular Care							
	Procedures	3,084 (32.0)	46,374 (29.7)	<0.001	3,084 (32.1)	3,092 (32.1)	0.902
	Medications	3,865 (40.2)	64,521 (41.3)	0.027	3,865 (40.2)	3,843 (39.9)	0.746

ICH, intracerebral haemorrhage; SD, standard deviation; yrs, years. p < 0.01

Table S8. Baseline characteristics n (%) of intracerebral haemorrhagic stroke patients with or without ischaemic heart diseases before and after propensity score matching.

		Before Propensity-Score Matched Population			After Propensity-Score Matched Population		
		Stroke-heart syndrome cohort (*n = 15,413*)	ICH cohort (*n = 160,978*)	*p* value	Stroke-heart syndrome cohort (*n = 14,961*)	ICH cohort (*n = 14,961*)	*p* value
Age (yrs) at diagnosis Mean (SD)		68.7 (14.0)	57.5 (22.9)	<0.001	68.7 (14.0)	68.8 (14.3)	0.923
Sex							
	Male	8,691 (58.1)	79,611 (52.8)	<0.001	8,691 (58.1)	8,693 (58.1)	0.981
	Female	5,780 (38.6)	68,279 (45.3)	<0.001	5,780 (38.6)	5,802 (38.8)	0.794
Ethnicity							
	White	9,802 (65.5)	92,185 (61.1)	<0.001	9,802 (65.5)	9,874 (66.0)	0.380
	Black or African American	1,869 (12.5)	20,464 (13.6)	<0.001	1,869 (12.5)	1,844 (12.3)	0.661
	Asian	504 (3.4)	6,846 (4.5)	<0.001	504 (3.4)	516 (3.4)	0.702
	Unknown	480 (3.2)	4,785 (3.2)	0.809	480 (3.2)	475 (3.2)	0.869
Comorbidities							
	Hypertensive Diseases	3,752 (25.1)	51,522 (34.2)	<0.001	3,752 (25.1)	3,732 (24.9)	0.789
	Diabetes Mellitus	1,568 (10.5)	21,464 (14.2)	<0.001	1,568 (10.5)	1,528 (10.2)	0.448
	Cerebrovascular Diseases	3,668 (24.5)	38,922 (25.8)	0.001	3,668 (24.5)	3,563 (23.8)	0.156
	Chronic Kidney Disease	820 (5.5)	11,826 (7.8)	<0.001	820 (5.5)	707 (4.7)	0.003
	Pulmonary Heart Disease and Diseases of Pulmonary Circulation	438 (2.9)	7,582 (5.0)	<0.001	438 (2.9)	368 (2.5)	0.012
Cardiovascular Care							
	Procedures	3,179 (21.2)	46,219 (30.6)	<0.001	3,179 (21.2)	3,122 (20.9)	0.419
	Medications	4,635 (31.0)	63,814 (42.3)	<0.001	4,635 (31.0)	4,694 (31.4)	0.462

ICH, intracerebral haemorrhage; SD, standard deviation; yrs, years. $p < 0.01$

Table S9. Baseline characteristics n (%) of intracerebral haemorrhagic stroke patients with or without Takotsubo syndrome before and after propensity score matching.

		Before Propensity-Score Matched Population			After Propensity-Score Matched Population		
		Stroke-heart syndrome cohort (*n = 409)*	ICH cohort (*n = 289,599*)	*p* value	Stroke-heart syndrome cohort (*n = 409*)	ICH cohort (*n = 409*)	*p* value
Age (yrs) at diagnosis Mean (SD)		60.5 (16.2)	59.5 (22.1)	0.360	60.5 (16.2)	59.6 (17.2)	0.434
Sex							
	Male	115 (28.1)	148,780 (53.3)	<0.001	115 (28.1)	116 (28.4)	0.938
	Female	289 (70.7)	122,711 (44.0)	<0.001	289 (70.7)	288 (70.4)	0.939
Ethnicity							
	White	278 (68.0)	168,112 (60.3)	0.001	278 (68.0)	284 (69.4)	0.651
	Black or African American	51 (12.5)	38,179 (13.7)	0.475	51 (12.5)	48 (11.7)	0.748
	Asian	12 (2.9)	12,576 (4.5)	0.125	12 (2.9)	14 (3.4)	0.690
	Unknown	18 (4.4)	9,598 (3.4)	0.287	18 (4.4)	19 (4.6)	0.866
Comorbidities							
	Hypertensive Diseases	109 (26.7)	102,257 (36.6)	<0.001	109 (26.7)	107 (26.2)	0.874
	Diabetes Mellitus	48 (11.7)	43,727 (15.7)	0.029	48 (11.7)	44 (10.8)	0.658
	Cerebrovascular Diseases	96 (23.5)	70,725 (25.3)	0.383	96 (23.5)	97 (23.7)	0.934
	Chronic Kidney Disease	26 (6.4)	26,338 (9.4)	0.033	26 (6.4)	23 (5.6)	0.658
	Pulmonary Heart Disease and Diseases of Pulmonary Circulation	22 (5.4)	15,503 (5.6)	0.876	22 (5.4)	18 (4.4)	0.517
Cardiovascular Care							
	Procedures	105 (25.7)	92,553 (33.2)	0.001	105 (25.7)	103 (25.2)	0.872
	Medications	147 (35.9)	129.998 (46.6)	<0.001	147 (35.9)	149 (36.4)	0.884

ICH, intracerebral haemorrhage; SD, standard deviation; yrs, years. $p < 0.01$

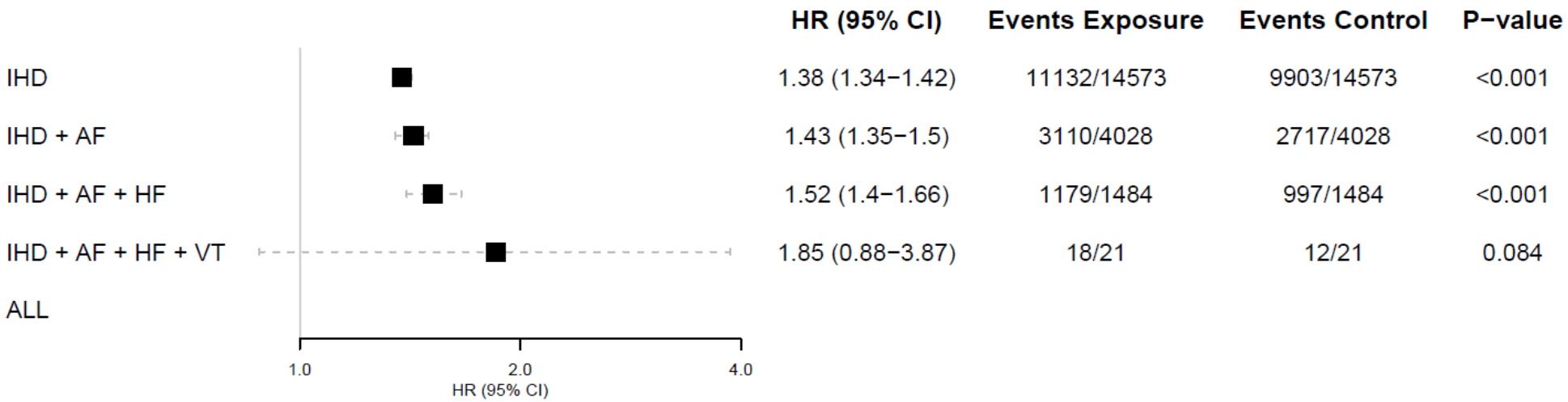

Figure S1. Hazard ratios and 95% confidence intervals for the risk of major adverse cardiovascular events over 5-year follow-up in patients with one or multiple newly diagnosed cardiovascular complications versus those who were not newly diagnosed with a cardiovascular complications 4-weeks post intracerebral haemorrhagic stroke.

AF, atrial fibrillation/flutter; CI, confidence interval; HF, heart failure; ICH, intracerebral haemorrhage; IHD, ischaemic heart disease; MACE, major adverse cardiovascular events; VT, severe ventricular arrhythmia.

Hazard ratio (HR), through Cox regression models, reported for propensity-score matched cohort.

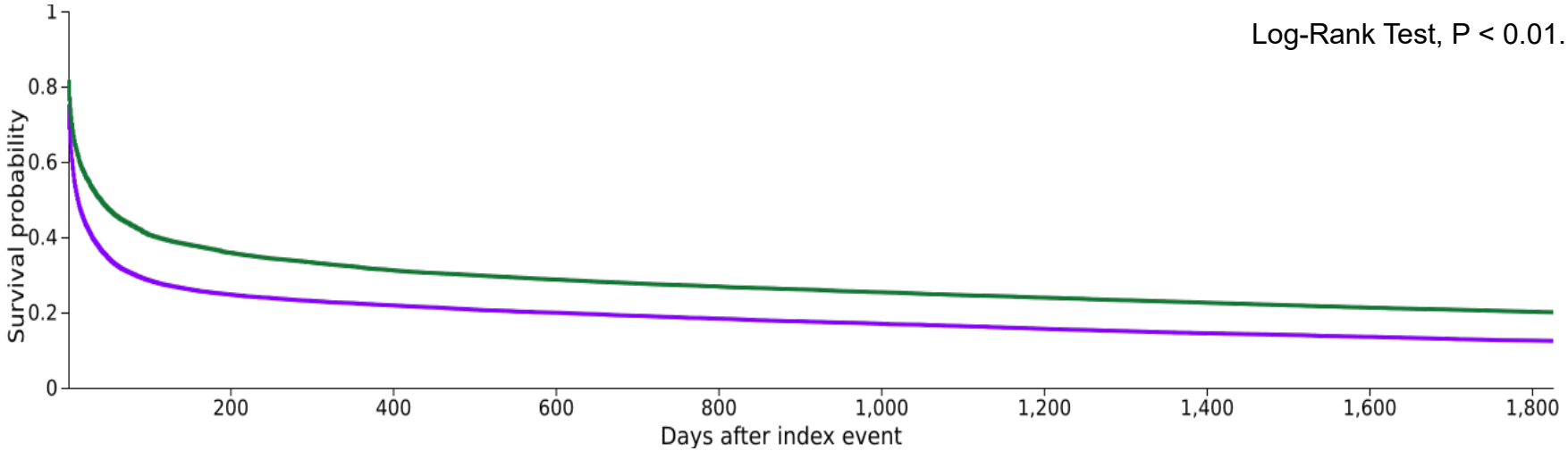

Figure S2. Kaplan-Meier diagram estimating the probability of the composites of 5-year major adverse cardiovascular events, in daily time intervals. Cumulative major adverse cardiovascular events occurring at 5-year follow up were 12.4% for stroke-heart syndrome cohort (n = 19,343, *green line*), and 20.1% for intracerebral haemorrhage only cohort (n = 17,343, *purple line*). Median days when composites of major adverse cardiovascular events occur for stroke-heart syndrome cohort and intracerebral haemorrhage only cohort were 13 days and 41 days, respectively.

ICH, intracerebral haemorrhage; MACE, major adverse cardiovascular events; SHS, stroke-heart syndrome

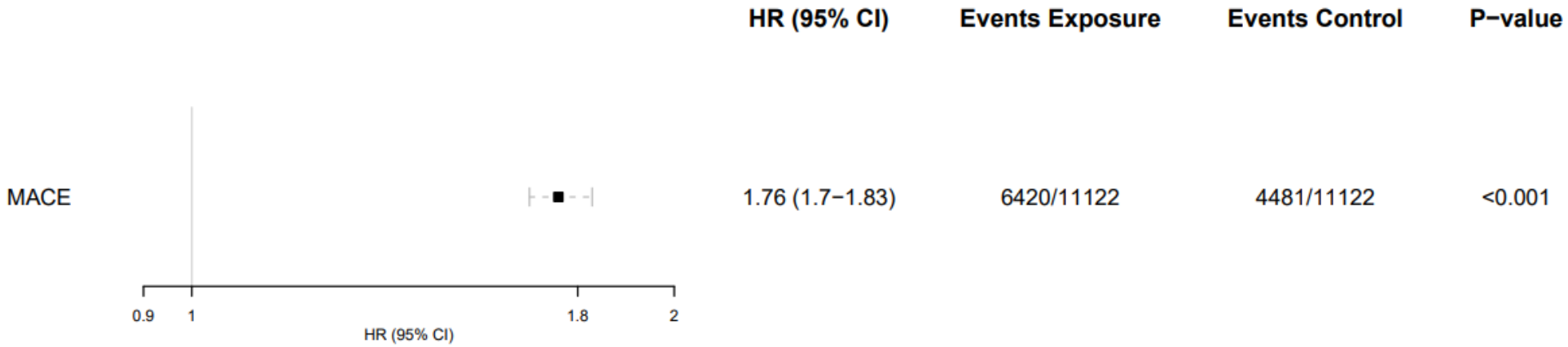

Figure S3. Hazard ratios and 95% confidence intervals for the risk of major adverse cardiovascular events over 5-year follow-up in stroke-heart syndrome cohort without pre-existing comorbidities (i.e., hypertensive diseases, chronic kidney disease, diabetes mellitus, cerebrovascular diseases, and pulmonary heart disease versus a stroke-heart syndrome cohort without comorbidities prior to intracerebral haemorrhagic stroke.

CI, confidence interval; ICH, intracerebral haemorrhage; MACE, major adverse cardiovascular events.

Hazard ratio (HR), through Cox regression models, reported for propensity-score matched cohort.