# Comparison of risk of serious cardiovascular events after haemorrhagic versus ischaemic stroke: a population-based study

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**Short title:** Cardiovascular risk after haemorrhagic versus ischemic stroke

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## ABSTRACT

**Background:** Patients with ischaemic stroke are considered a very-high risk population for subsequent cardiovascular events and guidelines recommend intensive preventive strategies. In contrast, there is no clear recommendation that patients with haemorrhagic stroke should also be regarded as a very-high cardiovascular risk population.

**Objective:** To compare the risk of subsequent cardiovascular morbidity/mortality between patients with incident haemorrhagic versus ischaemic stroke.

**Methods:** Patients aged ≥18 years with incident haemorrhagic or ischaemic stroke between 1998-2017, and no prior history of serious vascular event were identified from UK Clinical Practice Research Datalink (CPRD GOLD) linked to Hospital Episode Statistics (HES) data.

**Results:** The cohort included 32,091 patients with an overall follow-up of 381,237 person-years (median 11.8 years). After adjusting for potential confounders, patients with incident haemorrhagic stroke had no significantly different risk of subsequent cardiovascular morbidity compared with patients with incident ischaemic stroke – CHD [HR:0.86, 95%CI:0.56-1.32], recurrent stroke [HR:0.92, 95%CI:0.83-1.02], PVD [HR:1.15, 95%CI:0.56-2.38], or heart failure [HR:1.03, 95%CI:0.61-1.74]. Patients with incident haemorrhagic stroke had significantly higher risk of subsequent CVD-related mortality [HR:2.35, 95%CI:2.04-2.72] and all-cause mortality [HR: 2.16, 95%CI: 1.94-2.41].

Propensity-score matched analysis of 1,039 patients with haemorrhagic stroke and 1,039 with ischaemic stroke showed similar risk in subsequent cardiovascular morbidity – CHD [stratified hazard ratio (sHR):0.92, 95%CI:0.55-1.54], recurrent stroke [sHR:0.93, 95%CI:0.82-1.02)], PVD [sHR:1.04 95%CI:0.45-2.41], or heart failure [HR:0.71, 95%CI:0.39-1.27].

**Conclusions:** The risk of subsequent cardiovascular events is similar between patients with incident haemorrhagic or ischaemic stroke. Patients with previous haemorrhagic stroke should be regarded as a population at very-high risk of subsequent CVD.

***Keywords:*** haemorrhagic stroke; ischaemic stroke; propensity-score matching; electronic health records; real-world evidence; cardiovascular outcomes

## ABBREVIATIONS

| | |
|---|---|
| BMI | Body mass index |
| CHD | Coronary heart disease |
| CPRD | Clinical Practice Research Datalink |
| CVD | Cardiovascular disease |
| HDL-C | High-density lipoprotein cholesterol |
| HR | Hazard ratio |
| IMD | Index of Multiple Deprivation |
| LDL-C | Low-density lipoprotein cholesterol |
| MACE | Major adverse cardiovascular event |
| PS | Propensity score |
| PVD | Peripheral vascular disease |
| sHR | Stratified hazard ratio |

## SUMMARY TABLE

### What is known on this topic?

- Patients with ischaemic stroke are a very-high risk population for subsequent cardiovascular disease and current guidelines recommend intensive preventive strategies.
- There is no clear recommendation for patients with haemorrhagic stroke to be regarded to also be at a very-high risk of subsequent cardiovascular disease.

### What does this paper add?

- Patients with previous haemorrhagic stroke should be regarded as a very-high risk of subsequent cardiovascular events, similar to patients with previous ischaemic stroke.

## INTRODUCTION

Patients with ischemic stroke are considered a very-high risk population for subsequent cardiovascular events and current guidelines recommend intensive preventive strategies to reduce the cardiovascular risk.(1) In contrast, the amount of evidence about the overall cardiovascular risk in patients with haemorrhagic stroke is limited and there is no clear recommendation that these patients should be regarded as a population with very-high cardiovascular risk.

To date, there is no reliable evidence to compare the risk of future cardiovascular events in patients with haemorrhagic versus ischemic stroke and therefore, it is unclear whether patients with haemorrhagic stroke should be regarded as a population with very-high risk of subsequent cardiovascular disease (CVD). Using a large population-based cohort in the United Kingdom this study, therefore, aimed to compare the risk of subsequent cardiovascular morbidity and mortality outcomes between patients with incident haemorrhagic and ischaemic stroke after controlling for confounders or simulating inter-group differences in individual characteristics.

## METHODS

### Data availability

The data supporting the findings of this study are available from Clinical Practice Research Datalink (www.cprd.com). Restrictions apply to the availability of these data used under license for the current study, hence not publicly available.

### Data source

This prospective population-based cohort study used the UK Clinical Practice Research Datalink (CPRD) GOLD database of anonymised longitudinal primary care electronic health records,(2) linked to secondary care hospitalisation data (Hospital Episode Statistics [HES]),(3) national mortality data (Office for National Statistics [ONS]),(4) and social deprivation data (Index of Multiple Deprivation (IMD) 2015).(5) Patients included in CPRD GOLD database, from a network of general practices across the UK, are representative of the UK general population in terms of sex, age, and ethnicity,(2) thereby validating CPRD GOLD for epidemiological research. The study complied with the Declaration of Helsinki and was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency (Protocol number 19_023R).

### Study population

A cohort of patients with incident non-fatal stroke (at time of incident event) in either primary care (CPRD GOLD) or secondary care (HES) between 1 January 1998 and 31 December 2017 was identified. Details about this cohort were previously reported.(6) Patients with a prior record of coronary heart disease (CHD), peripheral vascular disease (PVD), or heart failure before incident stroke event were excluded. Patients were followed from the date of incident stroke diagnosis until they developed a major adverse cardiovascular event (MACE), died, ceased contributing data, or last data collection date (22 August 2019). The study flow diagram is shown in Figure 1.

**Cohort demographics and baseline characteristics**

Age was defined at the time of incident stroke. Ethnicity was categorised into six groups: Asian, Black, Mixed, Other, White and unknown.(7) To describe socioeconomic status, the English Index of Multiple Deprivation (IMD) 2015(5) linked to the patient's residential postcode was used. IMD is a weighted mean across seven domains, hence offers a single score to describe the concept of deprivation; categorised into quintiles (quintile 1 – least deprived group, to quintile 5 – most deprived group). Medication prescriptions (issue of prescription) at baseline were defined as a prescription within 12 months before incident stroke. For cholesterol (low density lipoprotein (LDL), high density lipoprotein (HDL) and total), body mass index (BMI), and blood pressure measures (diastolic and systolic), the most recent values/measures within 24 months before incident stroke were used. All other comorbidities were defined based on the latest record before incident stroke.

**Outcomes**

First subsequent coronary heart disease (CHD), recurrent stroke, PVD and heart failure after incident stroke were the primary outcomes. Composite MACE, cardiovascular-related mortality, and all-cause mortality was considered as a secondary outcome. MACE was defined as a composite of new onset coronary heart disease, recurrent stroke, peripheral vascular disease, and heart failure. Outcome events were based on records from the linked data sources (CPRD, HES or ONS registry).

**Statistical analysis**

Continuous variables were summarised as mean (SD) or median (IQR); nominal variables were presented as counts and valid percentages. Normal distribution was graphically assessed by histograms and P-P plots. Kruskal-Wallis test for continuous data and chi-squared test for categorical data were used to compare baseline

characteristics. The level of missing values ranged between 19.4% for blood pressure measures to 69.9% for LDL-C. Details on the proportion of missingness is provided in Supplemental Table I.

*Complete-case analysis*

The primary analysis was performed on the complete-case cohort and included two sub-analyses: one for the entire population of the complete-case cohort, and the other for a propensity-score matched population of the complete-case cohort. A multivariable probit regression model was used to calculate propensity scores for the conditional probability of classification (ischaemic versus haemorrhagic stroke) in 5,368 patients with ischaemic and 1,045 patients with haemorrhagic stroke. The propensity score (PS) matching model included age, sex, general practice, smoking status, socioeconomic status (IMD), blood pressure, BMI, HDL-C, LDL-C, diagnosis of atrial fibrillation, alcohol problem, cancer, dementia, diabetes mellitus, dyslipidaemia, hypertension, severe mental illness, transient ischaemic attack, family history of cardiovascular disease, a prescription of antihypertensive, anticoagulant, antidepressant, antiplatelet, diuretic, NSAIDS, opioids and potency of prescribed statin. Patients with incident haemorrhagic and ischaemic stroke (n=2,078) were matched using a 1:1 greedy matching algorithm of nearest neighbour with a calliper of 0.01 and no replacement – Supplemental Figures I, II, and Supplemental Table II.

Cox proportion hazards models were used to estimate Hazard ratio (HR) with 95% confidence interval (95% CI) for subsequent cardiovascular morbidity and mortality outcomes between patients with incident haemorrhagic and ischaemic stroke. Multivariable Cox models adjusting for pre-specified covariates based on relevant literature or biological plausibility [age at time of incident stroke, sex, socioeconomic status, smoking status, body mass index, blood pressure, cholesterols (high density lipoprotein, low density lipoprotein, and total), diagnosis of alcohol problem, atrial

fibrillation, cancer, chronic kidney disease, diabetes mellitus, dyslipidaemia, hypertension, transient ischaemic attack, a prescription of antihypertensive, anticoagulant, antidiabetic, and potency of prescribed statin] were used for the entire cohort (non-PS-matched). The proportional hazards assumption was assessed using Schoenfeld residuals. For composite MACE outcome, patients were censored at the time of the first outcome event. Cox regression models with shared frailty on matched sets were used for the PS-matched cohort, to account for 'cluster effect' within matched pairs.(8) Kaplan-Meier curves were calculated to determine outcomes segregated by incident stroke sub-type (haemorrhagic vs. ischaemic). The log-rank test was used to compare the equality of the cumulative incidence plots between the stroke sub-type groups in the full cohort, while the stratified log-rank was used in the PS-matched cohort.(9)

*Multiple imputation analysis in the overall cohort*

A multiple imputation analysis was done in the overall cohort which included two sub-analyses: one at the entire population of the overall cohort, and one at a propensity-score matched population of the overall cohort. To estimate missing values for BMI, systolic and diastolic blood pressures, HDL-C, LDL-C and total cholesterol levels, multiple imputation by chained equations was used to generate 10 imputed datasets using all the other available patient variables.(10) The imputed datasets were pooled into a single dataset using Rubin's rules.(11) The propensity score matching methodology was undertaken as previously described – Supplemental Figures III, IV, and Supplemental Table III. These additional analyses were performed to evaluate the robustness of the study findings due to potential bias from the use of imputed values for the analyses.

*Landmark analysis*

To minimise the potential impact of incident stroke severity on subsequent mortality during the early/subacute phase, further 3- and 6-months landmark analyses were performed – patients with subsequent outcomes within the landmark periods were excluded.

All statistical analyses were performed using Stata SE version 17 (StataCorp LP). An alpha level of 0.05 was used for all analysis and all tests were 2-tailed. No formal power calculations were performed as all available data from this large study with 32,091 patients and 9,218 events of interest was used.

## RESULTS

### Clinical characteristics

There were 32,091 patients who developed either incident haemorrhagic or ischaemic stroke events between 1-Jan-1998 and 31-Dec-2017 with 16,834 (52.5%) being women. Of these, 6,413 patients had complete data for all study variables – 1,045 (16.3%) had an incident haemorrhagic stroke and 5,368 (83.7%) had an incident ischaemic stroke event. The median age was 75 years. Patients with ischaemic stroke more often had diabetes mellitus or chronic kidney disease at time of incident stroke event (Supplementary Table IV). The overall follow-up for the study cohort was 381,237.92 patient-years, corresponding to a median of 11.8 years (IQR: 6.9 – 16.2).

### Complete-case analysis

*Entire population*

Of the 6,413 patients with incident stroke and complete data, 214 (3.3%) had a subsequent CHD outcome during follow-up [haemorrhagic: 24 (2.3%) vs ischaemic: 190 (3.5%)]; 3,140 (49.0%) had a recurrent stroke [haemorrhagic: 403 (38.6%) vs ischaemic: 2,737 (51.0%)]; 60 (0.9%) had PVD, and 134 (2.1%) had heart failure. After adjusting for potential confounders (Table 1), patients with incident haemorrhagic stroke had no significantly different risk of subsequent cardiovascular morbidity outcomes when compared with patients with incident ischaemic stroke – CHD [hazard ratio (HR), 0.86 (95% CI 0.56-1.32)]; recurrent stroke [HR, 0.92 (95% CI 0.83-1.02)], PVD [HR, 1.15 (95% CI 0.56-2.38)], or heart failure [HR, 1.03 (95% CI 0.61-1.74)].

Patients with incident haemorrhagic stroke had a significantly higher risk of subsequent CVD-related mortality [HR, 2.35 (95% CI 2.04-2.72)] and all-cause mortality [HR, 2.16 (95% CI 1.94-2.41)].

The cumulative incidence plots for the subsequent severe cardiovascular morbidity outcomes are presented in Figure 2.

*Propensity-score matched analysis*

For the propensity-score matched analysis of the complete-case population, 1,039 patients with haemorrhagic stroke were matched with 1,039 with ischaemic stroke. Risk of subsequent cardiovascular morbidity outcomes were not significantly different between patients with incident haemorrhagic stroke compared with those with incident ischaemic stroke – CHD [stratified hazard ratio (sHR), 0.92 (95% CI 0.55-1.54)]; recurrent stroke [sHR, 0.93 (95% CI 0.82-1.06)], PVD [sHR, 1.04 (95% CI 0.45-2.41)], or heart failure [HR, 0.71 (95% CI 0.39-1.27)].

The risk of subsequent mortality outcomes were significantly higher in patients with incident haemorrhagic stroke – cardiovascular-related mortality [sHR, 2.36 (95% CI 1.93-2.90)] and all-cause mortality [sHR, 2.24 (95% CI 1.92-2.62)]– Table 1.

**Multiple imputation analysis in the overall cohort**

*Entire population*

In this analysis, the overall study cohort of 32,091 patients with incident stroke event and with missing values imputed was used – 6,535 (20.5%) of these patients had an incident haemorrhagic stroke and 25,556 (79.6%) had an incident ischaemic stroke event. The characteristic of the overall cohort is presented in Supplemental Table V. After adjusting for potential confounders in the entire cohort, patients with incident haemorrhagic as compared with those with ischaemic stroke had lower risk of subsequent CHD [n=926 (2.9%), HR 0.67 (95% CI 0.55-0.82)] and an increased risk of subsequent CVD-related mortality [n=6,001 (18.7%), HR 2.26 (95% CI 2.13-2.39)], and all-cause mortality [n=10,675 (33.3%), HR 1.95 (95% CI 1.86-2.03)].

The cumulative incidence plots for cardiovascular morbidity and mortality outcomes are presented in Supplemental Figure V.

*Propensity-score matched population*

For the propensity-score matched analysis, 6,534 patients with haemorrhagic stroke were matched with 6,534 patients with ischaemic stroke. The risk of subsequent CHD remained lower, and mortality (both CVD-related and all-cause) outcomes remained significantly higher in patients with incident haemorrhagic stroke compared with those with incident ischaemic stroke – Table 2. The cumulative incidence plots for cardiovascular morbidity and mortality outcomes are presented in Supplemental Figure VI.

**Landmark-analysis**

In the landmark analyses at 3 and 6 months, 17,193 patients with subsequent outcomes occurring within 3 months and 19,021 within 6 months of incident stroke events were excluded, respectively. For both 3- and 6-months analysis, the risk of subsequent CHD remained significantly lower in patients with haemorrhagic stroke. Although the risk of subsequent mortality outcomes remained higher in patients with haemorrhagic stroke compared with ischaemic stroke patients, it was attenuated at both 3- and 6-month analyses – Table 2.

## DISCUSSION

Within a large population-based cohort with a long follow-up period, this study indicates that the risk of subsequent cardiovascular morbidity (CHD, recurrent stroke, PVD, and heart failure) was similar between patients with incident haemorrhagic or ischaemic stroke. Also, we found a significantly increased risk of subsequent mortality outcomes (CVD-related and all-cause) in patients with incident haemorrhagic stroke as compared to their counterparts with ischaemic stroke.

Previous studies reported rates of cardiovascular events in patients with haemorrhagic stroke, however, they were mostly hospital-based cohort studies which focused on selected outcomes over short follow-up duration.(12) Recently, an analysis of two population-based studies reported a rate of 7.9 serious vascular events (defined as non-fatal stroke or myocardial infarction, or vascular death) per 100 patient-years.(12) Another analysis of four population-based studies concluded that the rate of arterial ischemic events, ischemic stroke and myocardial infarction is 2-3 times higher in persons with previous intracerebral haemorrhage compared to persons without.(13) The use of hospital-based registry cohort as compared to population-based cohort could introduce selection bias in the estimates. The study analysis is the first large-scale population-based study to compare long-term cardiovascular prognosis between patients with ischemic or haemorrhagic stroke over a long follow-up and shows that the risk of subsequent cardiovascular events in patients with haemorrhagic stroke is similar to that in patients with ischemic stroke.

The study finding of higher cardiovascular- and overall mortality in patients with haemorrhagic stroke compared to ischemic stroke is consistent to previous reports(14,15). A plausible explanation of this finding is that haemorrhagic strokes are usually more severe than ischemic strokes, given that stroke severity is a major predictor of stroke mortality.(16) To minimise the potential impact of incident stroke severity on subsequent mortality, two landmark analyses at 3 and 6 months were

performed; the attenuation of mortality risk between the 3- and 6-month landmark analyses seems to supports this explanation.

The strength of this study is in the size and representativeness of the CPRD GOLD dataset(2), this large population-based study used linked primary care, hospital, and mortality records to compare differences in subsequent cardiovascular outcomes in the stroke subtypes. Additionally, the use of an incident cohort, reflects current practice and avoids the distorting influences of bias present in cohorts with prevalent major adverse cardiovascular events. There are limitations in this study which should be taken into consideration. Although multiple confounders were accounted for in the multivariable analyses performed for the entire cohort and also in the propensity score matching, there may have been other residual confounders that could have influenced the overall results of the study. The severity of incident stroke was not available in the electronic health records and hence, it was not accounted for in the landmark analysis at both 3 and 6 months after incident stroke event. Information on the phenotypic subtypes of intracerebral haemorrhage was not available in the dataset. In this study these phenotypic differences could not be accounted for in the analyses and subgroup analyses to assess differences in risk of subsequent outcomes within these phenotypic subtypes could not be done.

This finding highlights the need to implement a holistic preventive strategy in patients with haemorrhagic stroke aiming to reduce the overall cardiovascular risk rather than narrowly focusing solely on the prevention of a recurrent intracranial haemorrhage. Non-pharmaceutical interventions like weight reduction, reduction of salt intake, smoking cessation, and implementation of healthy dietary patterns constitute the cornerstone of this holistic approach. Additionally, optimization of pharmaceutical management of cardiovascular risk factors like arterial hypertension, high cholesterol levels, diabetes mellitus, and strategies to increase patient adherence and persistence to it, is of paramount importance to reduce overall cardiovascular risk. Anti-thrombotic

treatment is a challenging issue in patients with haemorrhagic stroke as the associated bleeding risk might counterbalance some of the conferred benefits(17). Despite a low risk of recurrent intracerebral haemorrhage was reported in The REstart or Stop Antithrombotics Randomised Trial (RESTART),(18) there are other ongoing studies that are assessing the efficacy and safety of different antithrombotic strategies in patients with previous intracranial haemorrhage.(19) In addition, new classes of anti-thrombotics are being developed like the FXIa inhibitors which showed to have promising safety profile in preliminary reports.(20) Moreover, lipid-lowering treatment (including statins, ezetimibe and PCSK9 inhibitors) is crucial for cardiovascular risk reduction,(21–24) however, statins seem to increase the risk of haemorrhagic stroke in a dose-dependent manner, whereas PCSK9 inhibitors do not.(25) This implies that perhaps PCSK9 inhibitors may be a preferred lipid-lowering class in patients with previous haemorrhagic stroke.(25)

In conclusion, the results of this large population-based study of patients with incident haemorrhagic or ischaemic stroke suggest that patients with previous haemorrhagic stroke should be regarded as a very-high risk population for future cardiovascular events, as their risk is similar to patients with previous ischaemic stroke. Given that approximately 2.9 million individuals worldwide have a haemorrhagic stroke annually,(26) there is an urgent need for optimization of currently available strategies and development of new ones aiming to reduce the overall cardiovascular risk in this very-high risk population.

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**Contributions**

RKA and GN were involved in the study conception. Analysis was done by RKA and GG. The manuscript was drafted by RKA.
All authors reviewed and approved the final manuscript. RKA is the guarantor.

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**Supplemental Materials**

Supplemental Figures I – VI

Supplemental Table I – V

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**TABLES**

Table 1. **Subsequent cardiovascular morbidity and mortality outcomes according to incident stroke sub-type for the entire and propensity-score matched complete case cohort**

| Outcomes | Entire study cohort (n=6,413) | | | | Propensity-score matched cohort (n=2,078) | | | |
|---|---|---|---|---|---|---|---|---|
| | **Entire cohort** 6,413 (100%) | **Ischaemic** 5,368 (83.7%) | **Haemorrhagic** 1,045 (16.3%) | ***p*-value** | **Cohort** n=2,078 (100%) | **Ischaemic** n=1,039 | **Haemorrhagic** n=1,039 | ***p*-value** |
| **Coronary heart disease** | | | | | | | | |
| Number (percent) | 214 (3.3) | 190 (3.5) | 24 (2.3) | 0.041 | 60 (2.9) | 36 (3.5) | 24 (2.3) | 0.116 |
| Follow-up time | 1.55 (0.22 – 3.79) | 1.66 (0.22 – 3.79) | 1.35 (0.39 – 3.81) | 0.9386 | 1.62 (0.29 – 4.34) | 2.17 (0.24 – 5.08) | 1.35 (0.39 – 3.81) | 0.4923 |
| Incident rate [a] | 1.18 (1.03 – 1.35) | 1.19 (1.03 – 1.37) | 1.07 (0.72 – 1.60) | - | 1.10 (0.85 – 1.42) | 1.11 (0.80 – 1.54) | 1.08 (0.72 – 1.61) | - |
| Hazard ratio (95% CI) | – | Reference | 0.86 (0.56 – 1.32) | 0.490 | | Reference | 0.92 (0.55 – 1.54) | 0.752 |
| **Recurrent stroke** | | | | | | | | |
| Number (percent) | 3,140 (49.0) | 2,737 (51.0) | 403 (38.6) | <0.001 | 927 (44.6) | 526 (50.6) | 401 (38.6) | <0.001 |
| Follow-up time | 0.06 (0.02 – 0.33) | 0.06 (0.02 – 0.34) | 0.05 (0.02 – 0.27) | 0.1597 | 0.06 (0.02 – 0.30) | 0.06 (0.02 – 0.36) | 0.05 (0.02 – 0.25) | 0.1840 |
| Incident rate [a] | 34.06 (32.89 – 35.28) | 33.84 (32.60 – 35.14) | 35.63 (32.32 – 39.29) | - | 33.35 (31.27 – 35.57) | 31.86 (29.25 – 34.70) | 35.54 (32.22 – 39.19) | - |
| Hazard ratio (95% CI) | – | Reference | 0.92 (0.83 – 1.02) | 0.131 | | Reference | 0.93 (0.82 – 1.06) | 0.267 |
| **Peripheral vascular disease** | | | | | | | | |
| Number (percent) | 60 (0.9) | 51 (1.0) | 9 (0.9) | 0.785 | 22 (1.1) | 13 (1.3) | 9 (0.9) | 0.391 |
| Follow-up time | 1.71 (0.85 – 3.79) | 1.73 (0.81 – 3.75) | 1.62 (1.16 – 4.47) | 0.7094 | 1.61 (1.08 – 4.67) | 1.51 (1.08 – 5.20) | 1.62 (1.16 – 4.47) | 0.9202 |
| Incident rate [a] | 0.32 (0.25 – 0.42) | 0.31 (0.24 – 0.41) | 0.40 (0.21 – 0.76) | - | 0.40 (0.26 – 0.60) | 0.39 (0.23 – 0.68) | 0.40 (0.21 – 0.77) | - |
| Hazard ratio (95% CI) | – | Reference | 1.15 (0.56 – 2.38) | 0.705 | | Reference | 1.04 (0.45 – 2.41) | 0.932 |
| **Heart failure** | | | | | | | | |
| Number (percent) | 134 (2.1) | 117 (2.2) | 17 (1.6) | 0.253 | 51 (2.5) | 34 (3.3) | 17 (1.6) | 0.016 |
| Follow-up time | 1.49 (0.41 – 3.41) | 1.50 (0.41 – 3.28) | 1.35 (0.60 – 3.41) | 0.7131 | 1.17 (0.54 – 3.75) | 1.14 (0.41 – 3.75) | 1.35 (0.60 – 3.41) | 0.5758 |
| Incident rate [a] | 0.73 (0.61 – 0.86) | 0.72 (0.60 – 0.87) | 0.75 (0.47 – 1.21) | - | 0.92 (0.70 – 1.21) | 1.04 (0.74 – 1.45) | 0.76 (0.47 – 1.22) | - |
| Hazard ratio (95% CI) | – | Reference | 1.03 (0.61 – 1.74) | 0.898 | | Reference | 0.71 (0.39 – 1.27) | 0.249 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Major adverse cardiovascular event** (composite) | | | | | | | | |
| Number (percent) | 3,548 (55.3) | 3,095 (57.7) | 453 (43.4) | <0.001 | 1,060 (51.0) | 609 (58.6) | 451 (43.4) | 0.213 |
| Follow-up time | 0.7 (0.02 – 0.68) | 0.08 (0.02 – 0.72) | 0.07 (0.02 – 0.45) | 0.1861 | 0.07 (0.02 – 0.65) | 0.08 (0.02 – 0.86) | 0.07 (0.02 – 0.45) | 0.0794 |
| Incident rate [a] | 41.97 (40.61 – 43.37) | 41.80 (40.35 – 43.29) | 43.16 (39.37 – 47.33) | - | 41.34 (38.92 – 43.90) | 40.14 (37.07 – 43.46) | 43.07 (39.28 – 47.24) | - |
| Hazard ratio (95% CI) | – | Reference | 0.93 (0.84 – 1.02) | 0.130 | | Reference | 0.92 (0.82 – 1.03) | 0.166 |
| **Cardiovascular-related mortality** | | | | | | | | |
| Number (percent) | 993 (15.5) | 726 (13.5) | 267 (25.6) | <0.001 | 398 (19.2) | 133 (12.8) | 265 (25.5) | <0.001 |
| Follow-up time | 0.05 (0.01 – 0.35) | 0.07 (0.02 – 0.67) | 0.02 (0.01 – 0.07) | 0.0001 | 0.02 (0.01 – 0.16) | 0.08 (0.01 – 0.54) | 0.02 (0.01 – 0.07) | 0.0001 |
| Incident rate [a] | 5.23 (4.92 – 5.57) | 4.36 (4.06 – 4.69) | 11.43 (10.14 – 12.89) | - | 6.99 (6.34 – 7.71) | 3.95 (3.33 – 4.68) | 11.40 (10.11 – 12.86) | - |
| Hazard ratio (95% CI) | – | Reference | 2.35 (2.04 – 2.72) | <0.001 | | Reference | 2.36 (1.93 – 2.90) | <0.001 |
| **All-cause mortality** | | | | | | | | |
| Number (percent) | 1,786 (27.9) | 1,346 (25.1) | 440 (42.1) | <0.001 | 680 (32.7) | 243 (23.4) | 437 (42.1) | <0.001 |
| Follow-up time | 0.18 (0.02 – 2.25) | 0.28 (0.04 – 2.88) | 0.05 (0.01 – 0.70) | 0.0001 | 0.10 (0.01 – 1.43) | 0.29 (0.02 – 2.81) | 0.05 (0.01 – 0.72) | 0.0001 |
| Incident rate [a] | 9.09 (8.68 – 9.52) | 7.83 (7.42 – 8.26) | 17.93 (16.33 – 19.68) | - | 11.48 (10.65 – 12.38) | 6.99 (6.16 – 7.92) | 17.88 (16.28 – 19.64) | - |
| Hazard ratio (95% CI) | – | Reference | 2.16 (1.94 – 2.41) | <0.001 | | Reference | 2.24 (1.92 – 2.62) | <0.001 |

Follow-up time: Time from incident stroke event to mortality outcome reported as median with interquartile range. CI, confidence interval; HR, hazard ratio

[a] Incident rate per 100 person-years.

Model adjusted for age at time of incident stroke, sex, socioeconomic status, smoking status, body mass index, blood pressure, cholesterols (high density lipoprotein, low density lipoprotein, and total), diagnosis of alcohol problem, atrial fibrillation, cancer, chronic kidney disease, diabetes mellitus, dyslipidaemia, hypertension, transient ischaemic attack, a prescription of antihypertensive, anticoagulant, antidiabetic, and potency of prescribed statin.

Stratified hazard ratio (that is, Cox regression models with shared frailty) reported for propensity-score matched cohort.

Table 2. **Subsequent cardiovascular morbidity and mortality outcomes according to incident stroke sub-type for the entire and propensity-score matched cohort with imputed values**

| Outcomes | Entire study cohort (n=32,091) | | | | Propensity-score matched cohort (n=13,068) | | | |
|---|---|---|---|---|---|---|---|---|
| | **Entire cohort** 32,091 (100%) | **Ischaemic** 25,556 (79.6%) | **Haemorrhagic** 6,535 (20.4%) | ***p*-value** | **Cohort** n=13,068 (100%) | **Ischaemic** n=6,534 | **Haemorrhagic** n=6,534 | ***p*-value** |
| **Coronary heart disease** | | | | | | | | |
| Number (percent) | 926 (2.9) | 822 (3.2) | 104 (1.6) | <0.001 | 328 (2.5) | 224 (3.4) | 104 (1.6) | <0.001 |
| Follow-up time | 1.34 (0.25 – 3.81) | 1.33 (0.25 – 3.81) | 1.38 (0.23 – 3.93) | 0.9280 | 1.43 (0.19 – 4.45) | 1.51 (0.17 – 4.60) | 1.38 (0.23 – 3.93) | 0.9674 |
| Incident rate [a] | 0.93 (0.88 – 1.00) | 1.00 (0.94 – 1.07) | 0.61 (0.50 – 0.74) | - | 0.83 (0.74 – 0.92) | 1.00 (0.88 – 1.14) | 0.61 (0.50 – 0.74) | - |
| Hazard ratio (95% CI) | – | Reference | 0.67 (0.55 – 0.82) | <0.001 | - | Reference | 0.60 (0.47 – 0.75) | <0.001 |
| **Recurrent stroke** | | | | | | | | |
| Number (percent) | 15,417 (48.0) | 12,818 (50.2) | 2,599 (39.8) | <0.001 | 5,908 (45.2) | 3,309 (50.6) | 2,599 (39.8) | <0.001 |
| Follow-up time | 0.07 (0.02 – 0.38) | 0.07 (0.02 – 0.39) | 0.07 (0.02 – 0.32) | 0.0106 | 0.07 (0.02 – 0.40) | 0.07 (0.02 – 0.50) | 0.07 (0.02 – 0.32) | 0.0019 |
| Incident rate [a] | 33.41 (32.88 – 33.94) | 33.59 (33.02 – 34.18) | 32.51 (31.29 – 33.79) | - | 32.21 (31.40 – 33.04) | 31.97 (30.90 – 33.08) | 32.52 (31.30 – 33.80) | - |
| Hazard ratio (95% CI) | – | Reference | 0.93 (0.90 – 0.98) | 0.002 | - | Reference | 0.96 (0.91 – 1.01) | 0.115 |
| **Peripheral vascular disease** | | | | | | | | |
| Number (percent) | 210 (0.7) | 183 (0.7) | 27 (0.4) | 0.007 | 72 (0.6) | 45 (0.7) | 27 (0.4) | 0.033 |
| Follow-up time | 1.71 (0.59 – 3.75) | 1.69 (0.57 – 3.51) | 2.26 (0.86 – 4.67) | 0.3759 | 1.77 (0.60 – 3.38) | 1.73 (0.33 – 2.58) | 2.26 (0.86 – 4.67) | 0.2090 |
| Incident rate [a] | 0.21 (0.18 – 0.24) | 0.22 (0.19 – 0.25) | 0.16 (0.11 – 0.23) | - | 0.18 (0.14 – 0.23) | 0.20 (0.15 – 0.26) | 0.16 (0.11 – 0.23) | - |
| Hazard ratio (95% CI) | – | Reference | 0.83 (0.55 – 1.25) | 0.369 | - | Reference | 0.78 (0.48 – 1.26) | 0.305 |
| **Heart failure** | | | | | | | | |
| Number (percent) | 584 (1.8) | 516 (2.0) | 68 (1.0) | <0.001 | 179 (1.4) | 111 (1.7) | 68 (1.0) | 0.001 |
| Follow-up time | 1.50 (0.39 – 4.08) | 1.49 (0.37 – 4.12) | 1.57 (0.58 – 3.72) | 0.5862 | 1.66 (0.42 – 4.52) | 1.70 (0.37 – 5.06) | 1.57 (0.58 – 3.72) | 0.8468 |
| Incident rate [a] | 0.58 (0.53 -0.63) | 0.62 (0.57 – 0.67) | 0.39 (0.31 – 0.50) | - | 0.45 (0.39 – 0.52) | 0.49 (0.40 – 0.59) | 0.39 (0.31 – 0.50) | - |
| Hazard ratio (95% CI) | – | Reference | 0.81 (0.62 – 1.04) | 0.098 | - | Reference | 0.80 (0.59 – 1.09) | 0.157 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Major adverse cardiovascular event** (composite) | | | | | | | | |
| Number (percent) | 17,137 (53.4) | 14,339 (56.1) | 2,798 (42.8) | <0.001 | 6,487 (49.6) | 3,689 (56.5) | 2,798 (42.8) | <0.001 |
| Follow-up time | 0.08 (0.02 – 0.67) | 0.08 (0.02 – 0.70) | 0.07 (0.02 – 0.48) | 0.0001 | 0.08 (0.02 – 0.66) | 0.09 (0.02 – 0.84) | 0.07 (0.02 – 0.48) | 0.0001 |
| Incident rate [a] | 40.29 (39.69 – 40.90) | 40.96 (40.30 – 41.64) | 37.19 (35.83 – 38.59) | - | 37.96 (37.05 – 38.90) | 38.57 (37.34 – 39.83) | 37.20 (35.84 – 38.60) | - |
| Hazard ratio (95% CI) | – | Reference | 0.91 (0.87 – 0.95) | <0.001 | - | Reference | 0.92 (0.88 – 0.97) | <0.001 |
| **Cardiovascular-related mortality** | | | | | | | | |
| Number (percent) | 6,001 (18.7) | 4,248 (16.6) | 1,753 (26.8) | <0.001 | 2,731 (20.9) | 978 (15.0) | 1,753 (26.8) | <0.001 |
| Follow-up time | 0.05 (0.01 – 0.34) | 0.08 (0.02 – 0.69) | 0.02 (0.01 – 0.07) | 0.0001 | 0.03 (0.01 – 0.16) | 0.08 (0.02 – 0.76) | 0.02 (0.01 – 0.07) | 0.0001 |
| Incident rate [a] | 5.79 (5.65 – 5.94) | 4.95 (4.81 – 5.10) | 9.84 (9.39 -10.31) | - | 6.64 (6.40 – 6.70) | 4.20 (3.94 – 4.47) | 9.84 (9.39 – 10.31) | - |
| Hazard ratio (95% CI) | – | Reference | 2.26 (2.13 – 2.39) | <0.001 | - | Reference | 2.12 (1.96 – 2.28) | <0.001 |
| **All-cause mortality** | | | | | | | | |
| Number (percent) | 10,675 (33.3) | 7,851 (30.7) | 2,824 (43.2) | <0.001 | 4,673 (35.8) | 1,849 (28.3) | 2,824 (43.2) | <0.001 |
| Follow-up time | 0.15 (0.02 – 2.02) | 0.24 (0.04 – 2.54) | 0.04 (0.01 – 0.41) | 0.0001 | 0.08 (0.01 – 1.27) | 0.25 (0.04 – 2.50) | 0.04 (0.01 – 0.41) | 0.0001 |
| Incident rate [a] | 9.91 (9.72 – 10.10) | 8.81 (8.62 – 9.01) | 15.19 (14.64 – 15.76) | - | 10.90 (10.59 – 11.22) | 7.62 (7.28 – 7.97) | 15.19 (14.64 – 15.76) | - |
| Hazard ratio (95% CI) | – | Reference | 1.95 (1.86 – 2.03) | <0.001 | - | Reference | 1.85 (1.75 – 1.96) | <0.001 |

Follow-up time: Time from incident stroke event to mortality outcome reported as median with interquartile range. CI, confidence interval; HR, hazard ratio

[a] Incident rate per 100 person-years.

Model adjusted for age at time of incident stroke, sex, socioeconomic status, smoking status, body mass index, blood pressure, cholesterols (high density lipoprotein, low density lipoprotein, and total), diagnosis of alcohol problem, atrial fibrillation, cancer, chronic kidney disease, diabetes mellitus, dyslipidaemia, hypertension, transient ischaemic attack, a prescription of antihypertensive, anticoagulant, antidiabetic, and potency of prescribed statin.

Stratified hazard ratio (that is, Cox regression models with shared frailty) reported for propensity-score matched cohort.

Table 3. **Landmark analysis at 3 and 6 months for subsequent cardiovascular mortality according to incident stroke sub-type for the entire cohort with imputed values**

| Outcomes | 3 months landmark analysis (n=14,898) | | | | 6 months landmark analysis (n=13,070) | | | |
|---|---|---|---|---|---|---|---|---|
| | **Entire cohort** 14,898 (100%) | **Ischaemic** 12,289 (82.5%) | **Haemorrhagic** 2,609 (17.5%) | ***p*-value** | **Cohort** 13,070 (100%) | **Ischaemic** 1,039 | **Haemorrhagic** 1,039 | ***p*-value** |
| **Cardiovascular-related mortality** | | | | | | | | |
| Number (percent) | 1,651 (11.1) | 1,386 (11.3) | 265 (10.2) | 0.098 | 1,364 (10.4) | 1,148 (10.6) | 216 (9.5) | 0.094 |
| Follow-up time | 2.12 (0.74 – 4.57) | 2.17 (0.75 – 4.55) | 2.02 (0.70 – 4.68) | 0.4117 | 2.91 (1.37 – 5.11) | 2.93 (1.42 – 5.08) | 2.83 (1.10 – 5.52) | 0.5865 |
| Hazard ratio (95% CI) | – | Reference | 1.19 (1.04 – 1.35) | 0.011 | | Reference | 1.17 (1.01 – 1.35) | 0.036 |
| **All-cause mortality** | | | | | | | | |
| Number (percent) | 4,723 (31.7) | 3,919 (31.9) | 804 (30.8) | 0.284 | 4,079 (31.2) | 3,399 (31.5) | 680 (29.8) | 0.106 |
| Follow-up time | 2.52 (0.93 – 5.15) | 2.55 (0.96 – 5.11) | 2.41 (0.80 – 5.27) | 0.2997 | 3.08 (1.49 – 5.65) | 3.07 (1.50 – 5.64) | 3.17 (1.43 – 5.78) | 0.0001 |
| Hazard ratio (95% CI) | – | Reference | 1.19 (1.10 – 1.29) | <0.001 | | Reference | 1.16 (1.07 – 1.26) | <0.001 |

Follow-up time: Time from incident stroke event to mortality reported as median with interquartile range.

CI, confidence interval; HR, hazard ratio

Model adjusted for age at time of incident stroke, sex, socioeconomic status, smoking status, body mass index, blood pressure, cholesterols (high density lipoprotein, low density lipoprotein, and total), diagnosis of alcohol problem, atrial fibrillation, cancer, chronic kidney disease, diabetes mellitus, dyslipidaemia, hypertension, transient ischaemic attack, a prescription of antihypertensive, anticoagulant, antidiabetic, and potency of prescribed statin.

**FIGURES**