Incidence and outcomes of cardiocerebral infarction: A cohort study of two national population-based registries

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Tables 2; Figures 3

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Abstract

Background

Cardiocerebral infarction (CCI), which is concomitant acute myocardial infarction (AMI) and acute ischemic stroke (AIS), is a rare but severe presentation. However, there are few data on CCI, and the treatment options are uncertain. We investigated the characteristics and outcomes of CCI compared to AMI or AIS alone.

Methods

We performed a retrospective cohort study of 120,531 AMI and AIS patients from the national stroke and AMI registries in Singapore. Patients were categorised into AMI only, AIS only, synchronous CCI (same day), and metachronous CCI (within one week). The primary outcome was all-cause mortality and secondary outcome was cardiovascular mortality. The mortality risks were compared using Cox regression. Multivariable models adjusted for baseline demographics, clinical variables and treatment for AMI or AIS.

Results

Of 127,919 patients identified, 120,531 (94.2%) were included. 74,219 (61.6%) patients had AMI only, 44,721 (37.1%) had AIS only, 625 (0.5%) had synchronous CCI, and 966 (0.8%) had metachronous CCI. The mean age was 67.7 (SD 14.0) years. Synchronous and metachronous CCI had higher risk of 30-day mortality (synchronous: adjusted HR [aHR] 2.41, 95%CI 1.77-3.28; metachronous: aHR 2.80, 95%CI 2.11-3.73) than AMI only and AIS only (synchronous: aHR 2.90, 95%CI 1.87-4.51; metachronous: aHR 4.36, 95%CI 3.03-6.27). The risk of cardiovascular mortality was higher in synchronous and metachronous CCI than AMI (synchronous:

aHR 3.03, 95%CI 2.15-4.28; metachronous: aHR 3.41, 95%CI 2.50-4.65) or AIS only (synchronous: aHR 2.58, 95%CI 1.52-4.36; metachronous: aHR 4.52, 95%CI 2.95-6.92). In synchronous CCI, AMI was less likely to be managed with PCI and secondary prevention medications (p<0.001) compared to AMI only.

Conclusions

Synchronous CCI occurred in 1 in 200 cases of AIS and AMI. Synchronous and metachronous CCI had higher mortality than AMI or AIS alone.

Non-standard Abbreviations and Acronyms

ACEi – angiotensin converting enzyme inhibitor

ACS – acute coronary syndrome

AHA/ASA – American Heart Association/American Stroke Association

aHR – adjusted hazard ratio

AIS – acute ischemic stroke

AMI – acute myocardial infarction

ARB – angiotensin receptor blocker

CABG – coronary artery bypass grafting

CCI – cardiocerebral infarction

EVT – endovascular therapy

NRDO – National Registry of Diseases Office

PCI – percutaneous coronary intervention

SMIR – Singapore Myocardial Infarction Registry

SSR – Singapore Stroke Registry

TIA – transient ischemic attack

Introduction

Cardiovascular diseases account for 32% of deaths globally, of which 85% are due to myocardial infarction (MI) and stroke.[1] Patients with acute MI (AMI) are at increased risk of acute ischemic stroke (AIS), with a prevalence of 11.1 ischemic strokes per 1000 MI during the index hospitalization and 21.4 per 1000 MI at 1 year.[2] The risk of AMI after stroke is approximately 1.7% annually.[3] Given the high incidence of both conditions, a substantial population may develop both AMI and AIS.[4] In the largest case series to date on 1683 AIS and 1983 AMI patients, the prevalence of cardiocerebral infarction (CCI) was 0.79%, with a reported incidence of 0.7-2.2%.[5] The terms synchronous and metachronous AMI and AIS have also been used, with the prior defined by AMI and AIS at the same time, and the later meaning AMI and AIS one after the other.[5]

The significance of the duration between AMI and AIS is not well-defined, and there are no guidelines on the management of CCI. Studies suggest that patients with both MI and stroke may have increased mortality, and the 2021 systematic review of CCI that included 44 cases of CCI found that 10 cases died after a median of 2 days.[4] Despite the severity of CCI, there is a lack of research into establishing the incidence, characteristics, treatment and outcomes of this relatively rare but important condition. Therefore, we performed a large observational study of the national population-based AMI and stroke registries, to investigate the characteristics and outcomes of synchronous (same-day) CCI and metachronous (within one week) CCI.

Methods

Design

The data that support the findings of this study are available from the corresponding author upon reasonable request. We performed a cohort study of consecutive patients with clinically diagnosed AMI and/or AIS from January 2007 to June 2018 through the linkage of two population-based registries. Patients identified from the national Singapore Stroke Registry (SSR) and Singapore MI Registry (SMIR) were linked using unique patient identifiers.[6]

Data sources

SSR and SMIR were national population-based registries maintained by the National Registry of Diseases Office (NRDO). The SSR received stroke case notifications from all public healthcare institutions via Hospital In-patient Discharge Summary, Ministry of Health MediClaim list and death certificates.[6] The SMIR included AMI cases diagnosed in all public hospitals, private hospitals, and AMI deaths that occurred at home certified by general practitioners.[7] Notification of all AMI cases to the NRDO were mandated by legislation in Singapore. All cases of AIS and AMI were confirmed by registry coordinators by viewing the medical records before extraction of relevant clinical information.

Exposures

AIS was defined as an acute focal or global neurological deficit lasting over 24 hours or leading to death, caused by vascular occlusion or stenosis.[8] AMI was diagnosed based on the Fourth Universal Definition of Myocardial Infarction.[9] The International Classification of Diseases 9th Revision Clinical Modification codes were used to identify stroke and AMI cases in the prior to 2012, while the ICD-10 Australian Modification were used for stroke and AMI cases diagnosed from 2012 onwards. In

patients with multiple episodes of stroke and/or MI, only the first episode was considered. As synchronous and metachronous CCI are not clearly defined in literature, we defined synchronous CCI as AMI and AIS within 24 hours, while metachronous CCI was defined as AMI and AIS within one week of each other. One week was selected, as the European Stroke Society guidelines recommend that intravenous thrombolysis is contraindicated if ST-segment elevation myocardial infarction (STEMI) occurred within one week, suggesting that a different management strategy is required.[10] Patients with AIS and AMI that were more than one week apart were excluded from the study due to possible differences in pathology.

Data that were extracted included: demographics, co-morbidities, medications, laboratory results, and outcomes. Patients were categorised into five groups: [1] AMI only, [2] stroke only, [3] synchronous CCI, and metachronous CCI subdivided into those with [4] AMI before AIS and [5] AIS before AMI.

Outcomes

The primary outcomes were all-cause mortality during in-hospital stay, within 30 days and within 1 year from onset of AMI or AIS. The secondary outcomes were cardiovascular mortality during in-hospital stay, within 30 days and within 1 year. Cardiovascular mortality was defined based on the 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials, including AMI, sudden cardiac death, death due to heart failure, stroke, cardiovascular procedures, and cardiovascular hemorrhage.[11] Outcomes were ascertained from the Singapore Registry of Births and Deaths, linked using unique patient identifiers. Notification of death to the

Singapore Registry of Births and Deaths is mandatory for all deaths that occur in the country.

Statistical analysis

The number of patients with AMI, AIS, synchronous and metachronous CCI were divided by the number of Singapore residents in the same period to derive the incidence rates. The mid-year population estimates were obtained from the Singapore Department of Statistics. The incidence rates were not age or sex adjusted. Demographics and clinical characteristics were compared using Kruskal-Wallis test for continuous variables and Chi-square test for categorical variables. The Shapiro-Wilk test was used to test if each continuous variable was normally distributed. Continuous variables were presented as median (interquartile range [IQR]), while categorical variables were presented as count (percentage).

The risks of primary and secondary outcomes were compared using univariable and multivariable Cox regression. The multivariable model included baseline demographics, clinical variables and treatment for AMI or AIS. Schoenfeld residuals found no violation of the proportional hazards assumption in Cox regression. The results were reported as hazard ratios (HR) with 95% confidence intervals (CI). For the analysis of cardiovascular death, competing risk from non-cardiovascular deaths were accounted for by using the Fine-Gray competing risk model.

Post-hoc pairwise comparisons were also performed. To control for type 1 error from multiple testing, the uncorrected p-values were multiplied by the number of pairwise comparisons to derive the eventual p-values.

Missing data were excluded from the multivariable analyses through case deletion without imputation to maintain data in its original form. A p-value of <0.05 was deemed statistically significant. All analyses were performed using StataSE 14. Ethics approval was obtained from the National Healthcare Group domain specific review board.

This study was conducted in line with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Results

Of the 120,531 patients included in this study (Figure S1), 74,219 (61.6%) had AMI only, 44,721 (37.1%) had AIS only, and 625 (0.5%) had synchronous CCI. Of the 966 (0.8%) patients with metachronous CCI, 515 (0.4%) had AMI before AIS, while 451 (0.4%) had AIS before AMI (Figure 1). The incidence of AMI only increased from 162.3 per 100,000 in 2007 to 202.8 per 100,000 in 2018, while the incidence of AIS only increased from 99.7 per 100,000 in 2007 to 123.4 in 2018 (Figure 2A). The incidence of CCI fluctuated between 0.5 and 2.0 per 100,000 in the same period (Figure 2B).

Baseline characteristics of included patients

Overall, 76,374 (63.4%) patients were male and their mean age was 67.7 (SD 14.0) years (Table 1). Patients with AMI only were more likely to be male and older than those with synchronous or metachronous CCI (Table S1). Interestingly, patients with synchronous CCI and AMI after AIS were less likely to receive percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) (p<0.001), aspirin (p<0.001), P2Y12 inhibitors (p<0.001), beta-blockers (p<0.001) and

angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) ($p<0.001$) than patients with AMI only and AMI before AIS.

Patients with AIS only were younger and more likely to be male than those with synchronous CCI and AIS before AMI (Table S2). Patients with AIS alone were the least likely to have atrial fibrillation (AF) ($p<0.001$), diabetes ($p<0.001$) and had the lowest median NIHSS on presentation ($p<0.001$). Patients with synchronous CCI had the highest rate of endovascular therapy (EVT) for AIS ($p<0.001$). Patients with AIS before AMI were most likely to have undergone thrombolysis, while those with AMI before AIS were least likely to have undergone thrombolysis ($p<0.001$).

Primary outcome: all-cause mortality

Within 1 year, 29.9% of patients with AMI only, 15.4% of AIS only, 56.3% of synchronous CCI, 50.7% of AMI before AIS, and 59.4% of AIS before AMI died (Tables 1 and 2, Figure 3). Compared to those with AMI only, those with synchronous CCI and AMI before AIS had significantly higher risk of 30-day mortality (synchronous CCI: adjusted HR [aHR] 2.41, 95% CI 1.77-3.28; AMI before AIS: aHR 2.80, 95% CI 2.11-3.73) and 1-year all-cause mortality (synchronous CCI: aHR 2.19, 95% CI 1.77-2.71; AMI before AIS: aHR 2.54, 95% CI 2.03-3.16) (Table 2).

Compared to AIS only patients, patients with synchronous CCI had higher risk of in-hospital (aHR 2.07, 95% CI 1.32-3.26), 30-day (aHR 2.90, 95% CI 1.87-4.51) and 1-year mortality (aHR 2.48, 95% CI 1.79-3.43). Similarly, patients with AIS before AMI were associated with higher risk of in-hospital (aHR 3.89, 95% CI 2.67-5.67), 30-day (aHR 4.36, 95% CI 3.03-6.27) and 1-year mortality (aHR 4.18, 95% CI 3.20-5.47) compared to AIS only patients.

Secondary outcome: cardiovascular mortality

The risk of cardiovascular mortality was the highest in patients with synchronous CCI (Tables 1 and 2, Figure 3). The aHR for synchronous CCI versus AMI only group for in-hospital cardiovascular mortality was 1.95 (95% CI 1.34-2.84), 30-day mortality was 3.03 (95% CI 2.15-4.28) and 1-year mortality was 2.56 (95% CI 1.96-3.35). Similarly, patients with AMI before AIS had higher in-hospital (aHR 1.86, 95% CI 1.25-2.75), 30-day (aHR 3.41, 95% CI 2.50-4.65) and 1-year (aHR 2.91, 95% CI 2.22-3.83) cardiovascular death than AMI only patients. Compared to AIS only patients, synchronous CCI was also associated with higher in-hospital cardiovascular mortality (aHR 2.18, 95% CI 1.29-3.70), 30-day mortality (aHR 2.58, 95% CI 1.52-4.36) and 1-year mortality (aHR 2.08, 95% CI 1.32-3.27). Cardiovascular mortality was significantly higher in AIS before AMI than AIS only group during hospitalisation (aHR 3.84, 95% CI 2.43-6.06), at 30-day (aHR 4.52, 95% CI 2.95-6.92) and at 1-year (aHR 5.05, 95% CI 3.59-7.10).

Risk of mortality in patients treated with PCI, EVT or thrombolysis

PCI was associated with reduced 30-day all-cause (aHR 0.66, 95% CI 0.56-0.77) and cardiovascular (aHR 0.74, 95% CI 0.61-0.90) mortality in patients with AMI only, even after stratification by age and sex (Table S3), but not in patients with synchronous CCI, metachronous CCI and AMI before AIS. In patients with AIS before AMI, EVT or thrombolysis was associated with lower in-hospital all-cause mortality (aHR 0.34, 95% CI 0.13-0.93) in the overall population and males, 30-day all-cause mortality (aHR 0.23, 95% CI 0.10-0.77) in the overall population and females, and 30-day cardiovascular mortality (aHR 0.26, 95% CI 0.10-0.67) in the overall population and females (Table S4).

Comparison of synchronous CCI and metachronous CCI

In a post-hoc analysis, we compared the characteristics of synchronous CCI and metachronous CCI (Table S5). Patients with synchronous CCI were older than those with AMI before AIS, with lower Killip class, lower proportion of diabetes, and were less likely to have PCI/CABG or be treated with aspirin, P2Y12 inhibitors, ACEi/ARB, beta-blockers. Compared to those with AIS before AMI, patients with synchronous CCI were more likely to be treated with aspirin, but less likely to receive thrombolytic therapy. There were no significant differences between synchronous and metachronous CCI for adjusted all-cause and cardiovascular mortality (Table S6).

Discussion

AMI and AIS are common and life-threatening conditions, and concomitant occurrence of both conditions are particularly severe but remains understudied. A previous systematic review of CCI performed in 2021 identified only 44 cases in the literature,[4] thus limiting our understanding of the prognosis, risk factors and treatment of this condition. We performed the largest cohort study in known literature of CCI, and defined synchronous and metachronous CCI to set a framework for further study. The main findings of this study are that approximately 1 in 200 cases of AMI and/or AIS were synchronous CCI, and the risk of all-cause mortality and cardiovascular mortality up to 1 year was higher in patients with synchronous and metachronous CCI than patients with AMI or AIS only.

Incidence and prevalence of CCI

The association of AMI and AIS has been observed for several decades. An analysis of the Global Registry of Acute Coronary Events found that in patients hospitalized with acute coronary syndrome (ACS), 0.9% developed AIS as an inpatient.[12] A meta-analysis of 58 studies on 131,299 patients showed a risk of MI of 1.67% post-AIS/transient ischemic attack (TIA) per year.[3] However, the prevalence of CCI is unknown due to its rarity and evidence largely relied on case series and case reports. In a previous study in Singapore by Yeo et al. including 555 AIS patients, 5 cases (0.9%) had CCI.[13] A cross-sectional study by de Castillo et al. on 1683 AIS and 1983 AMI patients found a synchronous CCI prevalence of 0.25%.[5] In our cohort of 120,531 patients, the prevalence of synchronous CCI was 0.5%, which was less susceptible to selection bias than previous smaller studies and case series. Despite a prevalence of 1 in 200 cases of AMI or AIS, there is a notable lack of guidance from international guidelines and greater research focus is needed to understand the causes and optimum management of CCI.

Mechanisms of CCI

Several mechanisms for CCI have been proposed. Left ventricular thrombus formation after AMI due to LV akinesia and dyskinesia, hypercoagulability and subendocardial changes may embolize and lead to ischemic strokes.[14] Thromboembolism to the coronary arteries may also occur simultaneously to cerebral vessels, one of the common cause of which is AF.[15] We identified that patients with synchronous (or same-day AIS and AMI) and metachronous CCI (AIS and AMI within 1 week) had higher proportions of AF compared to those with AIS alone, supporting this theory of cardiac thromboembolism. AF is predictive of severe stroke and early mortality, and cardioembolic stroke has highest mortality compared

to other subtypes.[16] We found that synchronous and metachronous CCI presented with higher NIHSS score and hence stroke severity, supporting the possibility of cardioembolism. It would be important to investigate the prevalence of cardioembolic stroke and benefit of cardiac monitoring in CCI.

Outcomes of CCI compared to AIS and AMI alone

While previous research reported that CCI patients have a high mortality rate,[5] none compared this to non-CCI patients or between patients with synchronous and metachronous CCI. De Castillo et al. reported an all-cause mortality rate of 45%.[5] In our larger cohort, we found that 1-year all-cause mortality was 56.3% in patients with synchronous CCI, significantly higher than patients with AMI only (29.9%) and AIS only (15.4%), although due to the observational nature, only correlation but not causation could be established.

Previous research into AMI and AIS consistently found higher mortality than patients with MI or stroke alone, but comparison of outcomes between synchronous and metachronous CCI requires further research. In 7,930 patients with ACS in the Middle East, 0.70% developed in-patient stroke and had increased risk of in-hospital and 1-year mortality.[17] Vice versa, patients with post-stroke MI had increased risk of death in large cohort studies for up to 10 years of follow-up.[18] We similarly reported a higher in-hospital, 30-day and 1-year all-cause and cardiovascular mortality in patients with metachronous CCI. Post-hoc direct comparisons of synchronous and metachronous CCI did not show any significant differences after adjusting for confounding factors, requiring further investigation.

Treatment of CCI

Patients with AMI complicated by in-patient AIS were less likely to be treated with evidence-based therapies for ACS, such as dual antiplatelet therapy (DAPT), thrombolytic therapy or PCI in previous studies.[17] This was similarly shown in our study, where patients with synchronous CCI and AIS before AMI were less likely to receive PCI/CABG, DAPT and secondary prevention medications. Based on consensus opinion of experts, in synchronous CCI, the American Heart Association/American Stroke Association (AHA/ASA) scientific statement recommend that treatment with IV alteplase at the stroke dose of maximum 0.9mg/kg (lower than the MI dose) followed by PCI is reasonable.[19] Evidence from this study generally supports the use of PCI in metachronous CCI, although there was no significant reduction in mortality in synchronous CCI likely due to the subgroup analysis being under-powered.

EVT for stroke due to large vessel occlusion and perfusion mismatch in CCI was not considered in the AHA/ASA recommendations. In our cohort, patients with synchronous CCI had the highest rate of EVT, compared to patients with AIS alone or metachronous CCI. EVT and thrombolysis in patients with AIS before AMI was associated with lower in-hospital all-cause mortality and 30-day all-cause and cardiovascular mortality in our study. This supports a role for EVT and thrombolysis in metachronous CCI in selected cases.

Based on the current literature and our experience, we propose that initially, patients with CCI should be assessed for IV thrombolysis at 0.9 mg/kg, with consideration for EVT and PCI subsequently.[13] The decision for PCI versus EVT first should be based on the location of occlusion in the coronary or cerebral vessels, and service availability.[13] Further studies are needed to investigate the efficacy and

safety of these interventions in CCI, as well as the specific timing and sequence of interventions.

Strengths and Limitations

A major strength of this study was that data from two large population-based registries over more than a decade were analysed, resulting in the largest cohort of CCI patients in literature. The case coverage for AMI was high as it is mandatory for all healthcare institutions to report AMI to SMIR, and data quality was maintained by regular audits. As the SSR only covered AIS treated by the public healthcare institutions, there could be an underestimation of the incidence of CCI. However, an estimated >90% of the stroke cases were treated by the public healthcare institutions.[20]

As this is an observational study, which may be susceptible to unidentified confounding factors and limited by the factors captured by the registries, causation between CCI and mortality cannot be definitively established. There is potential loss to follow-up due to people migrating and dying outside of Singapore, but this is likely to affect each exposure arm equally. Our study outcomes were limited to 1-year mortality, and further research with longer follow up duration may be beneficial to investigate the long-term mortality. Results from the coronary angiography and neuroimaging were not available, and we did not investigate the details regarding the individual CCI cases. Detailed clinical data for CCI cases would be important in future studies for more comprehensive understanding of the etiology and management of CCI. We identified that much fewer underwent PCI in CCI compared to patients with AMI only, suggesting that PCI was underused in patients that presented with synchronous CCI or AIS before AMI. The clinical reasoning behind

this was not investigated. The impact of therapies and specific timing or dosages on mortality requires further investigation.

Conclusions

In this large cohort study of 120,531 patients from two linked national registries, we found that 1 in 200 cases of AIS and AMI were synchronous CCI. Patients with synchronous and metachronous CCI had higher all-cause and cardiovascular mortality than patients with AMI or AIS alone. Further research with prospective detailed clinical data on cases of CCI is needed to investigate the optimal treatment for CCI, and mechanistic studies with particular focus on cardioembolism are of clinical importance.

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Supplemental Material

Tables S1-S6

Figure S1

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Figure legends

Central Illustration: Summary of the prevalence and outcomes of synchronous and metachronous cardiocerebral infarction

Abbreviations: aHR – adjusted hazards ratio; AIS – acute ischemic stroke; AMI – acute myocardial infarction; CCI – cardiocerebral infarction; MCCI – metachronous cardiocerebral infarction; SCCI – synchronous cardiocerebral infaction

Figure 1: Proportion of cardiocerebal infarction types across the study period

Abbreviations: MI – myocardial infarction

Figure 2: Incidence rate of (A) acute myocardial infarction only and acute ischemic stroke only and (B) synchronous and metachronous cardiocerebral infarction across the study period

Abbreviations: MI – myocardial infarction

Figure 3: Kaplan-Meier survival curves for all-cause and cardiovascular mortality

Abbreviations: AIS – acute ischemic stroke; AMI – acute myocardial infarction; CV – cardiovascular

Table 1: Demographic and clinical characteristics of patients

	AMI only N=74219	AIS only N=44721	AMI and AIS same day N=625	AMI before AIS N=515	AIS before AMI N=451	p-value*
Duration between AMI and AIS, days, median (IQR)	NA	NA	NA	3 (1-5)	2 (1-4)	<0.001
Male, n (%)	50004 (67.4)	25549 (57.1)	314 (50.2)	296 (57.5)	211 (46.8)	<0.001
Race, n (%)						
Chinese	50355 (67.8)	34720 (77.6)	448 (71.7)	334 (64.9)	328 (72.7)	<0.001
Malay	13565 (18.3)	6423 (14.4)	125 (20.0)	118 (22.9)	89 (19.7)	
Indian	9182 (12.4)	2814 (6.3)	40 (6.4)	54 (10.5)	29 (6.4)	
Others	1117 (1.5)	764 (1.7)	12 (1.9)	9 (1.7)	5 (1.1)	
AMI risk factors						
Age, median (IQR)	67.3 (56.8-78.7)	NA	75.3 (63.6-83.5)	69.8 (59.8-79.0)	76.6 (66.3-83.9)	<0.001
History of hypertension, n (%)	48656 (67.5)	NA	472 (75.8)	357 (69.3)	362 (80.4)	<0.001
History of diabetes, n (%)	29232 (40.6)	NA	243 (39.0)	247 (48.0)	210 (46.7)	<0.001
History of hyperlipidemia, n (%)	39921 (55.5)	NA	316 (50.7)	280 (54.4)	267 (59.5)	0.032
Smoking status, n (%)						
Current	19384 (27.6)	NA	110 (19.2)	128 (25.5)	62 (14.7)	<0.001
Former	12957 (18.5)	NA	86 (15.0)	67 (13.3)	69 (16.4)	
Never	37814 (53.9)	NA	377 (65.8)	308 (61.2)	290 (68.9)	
Killip class on admission, n (%)						
I	56653 (78.4)	NA	520 (83.5)	339 (65.8)	411 (91.7)	<0.001
II	8179 (11.3)	NA	48 (7.7)	84 (16.3)	22 (4.9)	
III	5211 (7.2)	NA	41 (6.6)	64 (12.4)	13 (2.9)	
IV	2220 (3.1)	NA	14 (2.2)	28 (5.4)	2 (0.5)	
Serum creatinine in µmol, median (IQR)	98 (78-145)	NA	102 (80-147)	109 (82-150)	99 (75-142)	0.019
Haemoglobin in g/dL, median (IQR)	13.1 (11.1-14.7)	NA	13.1 (11.5-14.4)	12.8 (10.7-14.4)	12.8 (11.4-14.1)	0.015
Low-density lipoprotein in mmol/l, median (IQR)	3.1 (2.3-3.9)	NA	3.0 (2.2-4.1)	3.0 (2.4-3.9)	2.8 (2.2-3.8)	0.723
HbA1c in %, median (IQR)	6.2 (5.6-7.6)	NA	6.2 (5.7-7.6)	6.6 (5.8-8.9)	6.4 (5.7-7.7)	<0.001
Type of AMI, n (%)						
STEMI	22104 (29.8)	NA	102 (16.3)	163 (31.7)	57 (12.6)	<0.001

NSTEMI	44624 (60.1)	NA	480 (76.8)	327 (63.5)	338 (74.9)	
Unclassified	7491 (10.1)	NA	43 (6.9)	25 (4.8)	56 (12.4)	
LVEF<50% during hospitalization, n (%)	29632 (54.0)	NA	254 (56.3)	316 (71.7)	169 (52.7)	<0.001
In-hospital AMI treatment						
PCI/CABG, n (%)	29558 (39.8)	NA	27 (4.3)	121 (23.5)	16 (3.6)	<0.001
Aspirin, n (%)	56491 (78.4)	NA	425 (68.0)	395 (76.7)	255 (56.5)	<0.001
P2Y12 inhibitor, n (%)	52694 (73.1)	NA	339 (54.2)	366 (71.1)	234 (51.9)	<0.001
Beta-blocker, n (%)	52061 (72.2)	NA	332 (53.1)	372 (72.2)	246 (54.6)	<0.001
ACEI/ARB, n (%)	41134 (57.1)	NA	228 (36.5)	257 (49.9)	146 (32.4)	<0.001
Lipid lowering drug, n (%)	58888 (81.7)	NA	507 (81.1)	431 (83.7)	356 (78.9)	0.286
AIS risk factors						
Age, median (IQR)	NA	68.2 (58.6-78.0)	75.4 (63.6-83.5)	69.8 (59.8-79.0)	76.6 (66.3-83.9)	<0.001
Hypertension, n (%)	NA	35738 (79.9)	521 (83.4)	405 (78.6)	383 (84.9)	0.007
Diabetes, n (%)	NA	18348 (41.0)	288 (46.1)	280 (54.4)	238 (52.8)	<0.001
Hyperlipidemia, n (%)	NA	39299 (87.9)	502 (80.3)	424 (82.3)	381 (84.5)	<0.001
Atrial fibrillation/flutter, n (%)	NA	8372 (18.7)	193 (30.9)	146 (28.4)	177 (39.3)	<0.001
Current/former smoker, n (%)	NA	16570 (38.5)	209 (36.4)	204 (41.4)	140 (32.6)	0.031
Baseline NIHSS, median (IQR)	NA	4 (1-8)	13 (5-23)	12 (5-21)	12 (6-19)	<0.001
In-hospital AIS teatment						
Endovascular therapy, n (%)	NA	713 (1.6)	23 (3.7)	9 (1.8)	11 (2.4)	<0.001
Thrombolytic agent, n (%)	NA	2391 (5.4)	43 (6.9)	15 (2.9)	53 (11.8)	<0.001
Anti-platelet, n (%)	NA	39625 (88.6)	505 (80.8)	409 (79.4)	358 (79.4)	<0.001
Anti-coagulant, n (%)	NA	5776 (12.9)	184 (29.4)	159 (30.9)	145 (32.2)	<0.001
Outcomes						
In-hospital all-cause mortality, n (%)	11329 (15.7)	2695 (6.0)	222 (35.5)	177 (34.4)	173 (38.4)	<0.001
30-day all-cause mortality, n (%)	14347 (19.3)	3042 (6.8)	232 (37.1)	180 (35.0)	178 (39.5)	<0.001
1-year all-cause mortality, n (%)	22167 (29.9)	6875 (15.4)	352 (56.3)	261 (50.7)	268 (59.4)	<0.001
In-hospital cardiovascular mortality, n (%)	7079 (9.8)	2116 (4.7)	200 (32.0)	143 (27.8)	140 (31.0)	<0.001
30-day cardiovascular mortality, n (%)	9707 (13.1)	2314 (5.2)	206 (33.0)	147 (28.5)	146 (32.4)	<0.001

1-year cardiovascular mortality, n (%)	13165 (17.7)	3943 (8.8)	274 (43.8)	190 (36.9)	198 (43.9)	<0.001

*p-value of the comparison among the 5 study groups

Abbreviations: ACEI - angiotensin-converting enzyme inhibitors; AIS - acute ischemic stroke; AMI – acute myocardial infarction; ARB - angiotensin receptor blockers; CABG - coronary artery bypass graft; HbA1c - hemoglobin A1c; IQR – interquartile range; LVEF – left ventricular ejection fraction; NA – not applicable; NIHSS - National Institutes of Health Stroke Scale; NSTEMI - non-ST segment elevation myocardial infarction; PCI – percutaneous coronary intervention; STEMI - ST segment elevation myocardial infarction

Table 2: Risk of death among patients with cardiocerebral infarction (same-day) and AMI and AIS within one week of each other, compared to patients with AMI only and patients with AIS only

	AMI only	AMI and AIS same day	AMI before AIS	AIS only	AMI and AIS same day	AIS before AMI
In-hospital all-cause mortality, n (%)	11329 (15.7)	222 (35.5)	177 (34.4)	2695 (6.0)	222 (35.5)	173 (38.4)
Unadjusted HR (95% CI)	Reference	1.45 (1.26-1.66)	1.27 (1.10-1.48)	Reference	2.96 (2.57-3.41)	3.86 (3.31-4.51)
*Adjusted HR (95% CI)	Reference	1.24 (0.90-1.71)	1.29 (0.97-1.72)	Reference	2.07 (1.32-3.26)	3.89 (2.67-5.67)
30-day all-cause mortality, n (%)	14347 (19.3)	232 (37.1)	180 (35.0)	3042 (6.8)	232 (37.1)	178 (39.5)
Unadjusted HR (95% CI)	Reference	2.60 (2.28-2.97)	2.40 (2.07-2.78)	Reference	6.53 (5.70-7.49)	7.18 (6.17-8.35)
*Adjusted HR (95% CI)	Reference	2.41 (1.77-3.28)	2.80 (2.11-3.73)	Reference	2.90 (1.87-4.51)	4.36 (3.03-6.27)
1-year all-cause mortality, n (%)	22167 (29.9)	352 (56.3)	261 (50.7)	6875 (15.4)	352 (56.3)	268 (59.4)
Unadjusted HR (95% CI)	Reference	2.61 (2.34-2.90)	2.25 (1.99-2.55)	Reference	5.22 (4.68-5.82)	5.84 (5.17-6.60)
*Adjusted HR (95% CI)	Reference	2.19 (1.77-2.71)	2.54 (2.03-3.16)	Reference	2.48 (1.79-3.43)	4.18 (3.20-5.47)
In-hospital cardiovascular mortality, n (%)	7079 (9.8)	200 (32.0)	143 (27.8)	2116 (4.7)	200 (32.0)	140 (31.0)
Unadjusted HR (95% CI)	Reference	2.56 (2.21-2.96)	2.06 (1.75-2.42)	Reference	3.68 (3.13-4.33)	4.07 (3.40-4.86)
*Adjusted HR (95% CI)	Reference	1.95 (1.34-2.84)	1.86 (1.25-2.75)	Reference	2.18 (1.29-3.70)	3.84 (2.43-6.06)
30-day cardiovascular mortality	9707 (13.1)	206 (33.0)	147 (28.5)	2314 (5.2)	206 (33.0)	146 (32.4)
Unadjusted HR (95% CI)	Reference	3.83 (3.35-4.39)	3.28 (2.82-3.81)	Reference	7.42 (6.41-8.57)	7.47 (6.34-8.80)
*Adjusted HR (95% CI)	Reference	3.03 (2.15-4.28)	3.41 (2.50-4.65)	Reference	2.58 (1.52-4.36)	4.52 (2.95-6.92)
1-year cardiovascular mortality	13165 (17.7)	274 (43.8)	190 (36.9)	3943 (8.8)	274 (43.8)	198 (43.9)
Unadjusted HR (95% CI)	Reference	3.66 (3.24-4.12)	2.98 (2.59-3.42)	Reference	6.37 (5.61-7.24)	6.53 (5.65-7.54)
*Adjusted HR (95% CI)	Reference	2.56	2.91	Reference	2.08	5.05

		(1.96-3.35)	(2.22-3.83)		(1.32-3.27)	(3.59-7.10)

*For AMI only, AMI and AIS same day, and AMI before AIS, the following variables were included: gender, ethnicity, age, hypertension, diabetes, hyperlipidemia, smoking, Killip class on admission, creatinine, hemoglobin, total cholesterol, HbA1c, AMI type, LVEF<50% during hospitalization, PCI/CABG, aspirin, P2Y12 inhibitor, beta-blocker, ACEI/ARB and lipid lowering drug given during hospitalization

For AIS only, AMI and AIS same day, and AIS before AMI, the following variables were included: gender, ethnicity, age, hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking, NIHSS score on admission, surgery or endovascular therapy, thrombolytic agent, anti-platelet and anti-coagulant given during hospitalization

Abbreviations: ACEI - angiotensin-converting enzyme inhibitors; AIS - acute ischemic stroke; AMI – acute myocardial infarction; ARB - angiotensin receptor blockers; CABG - coronary artery bypass graft; CCI – cardiocerebral infarction; CI – confidence interval; HbA1c - hemoglobin A1c; HR – hazard ratio; NIHSS - National Institutes of Health Stroke Scale