Journal of the American Heart Association

ORIGINAL RESEARCH

Heart-Brain Team Approach of Acute Myocardial Infarction Complicating Acute Stroke: Characteristics of Guideline-Recommended Coronary Revascularization and Antithrombotic Therapy and Cardiovascular and Bleeding Outcomes

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BACKGROUND: Acute myocardial infarction (AMI) infrequently occurs after acute stroke. The Heart-brain team approach has a potential to appropriately manage this poststroke cardiovascular complication. However, clinical outcomes of AMI complicating acute stroke (AMI-CAS) with the heart-brain team approach have not been characterized. The current study investigated cardiovascular outcomes in patients with AMI-CAS managed by a heart-brain team.

METHODS AND RESULTS: We retrospectively analyzed 2390 patients with AMI at our institute (January 1, 2007–September 30, 2020). AMI-CAS was defined as the occurrence of AMI within 14 days after acute stroke. Major adverse cerebral/cardiovascular events (cardiac-cause death, nonfatal myocardial infarction, and nonfatal stroke) and major bleeding events were compared in subjects with AMI-CAS and those without acute stroke. AMI-CAS was identified in 1.6% of the subjects. Most AMI-CASs (37/39=94.9%) presented ischemic stroke. Median duration of AMI from the onset of acute stroke was 2 days. Patients with AMI-CAS less frequently received primary percutaneous coronary intervention (43.6% versus 84.7%; $P<0.001$) and dual-antiplatelet therapy (38.5% versus 85.7%; $P<0.001$), and 33.3% of them did not receive any antithrombotic agents (versus 1.3%; $P<0.001$). During the observational period (median, 2.4 years [interquartile range, 1.1–4.4 years]), patients with AMI-CAS exhibited a greater likelihood of experiencing major adverse cerebral/cardiovascular events (hazard ratio [HR], 3.47 [95% CI, 1.99–6.05]; $P<0.001$) and major bleeding events (HR, 3.30 [95% CI, 1.34–8.10]; $P=0.009$). These relationships still existed even after adjusting for clinical characteristics and medication use (major adverse cerebral/cardiovascular event: HR, 1.87 [95% CI, 1.02–3.42]; $P=0.04$; major bleeding: HR, 2.67 [95% CI, 1.03–6.93]; $P=0.04$).

CONCLUSIONS: Under the heart-brain team approach, AMI-CAS was still a challenging disease, reflected by less adoption of primary percutaneous coronary intervention and antithrombotic therapies, with substantially elevated cardiovascular and major bleeding risks. Our findings underscore the need for a further refined approach to mitigate their ischemic/bleeding risks.

Key Words: acute myocardial infarction ■ acute stroke ■ antithrombotic therapy ■ bleeding ■ heart-brain team approach

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.027156

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In the current analysis of 2390 subjects with acute myocardial infarction, 1.6% of acute myocardial infarctions occurred following acute stroke, and patients with acute myocardial infarction complicating acute stroke (AMI-CAS) were less likely to receive the guideline-recommended coronary revascularization and antithrombotic therapies under the heart-brain team approach.
- Primary percutaneous coronary intervention and any antithrombotic therapy were not conducted in 56.4% and 33.3% of patients with AMI-CAS, respectively.
- During the 2.4-year observational period, AMI-CAS was associated with 1.87- and 2.67-fold elevated risks of cardiovascular and major bleeding events, respectively, compared with acute myocardial infarctions without acute stroke.

What Are the Clinical Implications?

- The heart-brain team approach has the potential to appropriately manage AMI-CAS, but difficulties still exist to commence guideline-recommended therapies in a considerable proportion of patients with AMI-CAS.
- Less adoption of primary percutaneous coronary intervention and antithrombotic therapy and a substantially elevated risk of cardiovascular/bleeding events underscore the need for a further refined heart-brain team approach to mitigate both ischemic and bleeding risks of AMI-CAS.
- In addition to shared decision making with cardiologists and neurologists, shorter duration of antithrombotic therapy and more adoption of established medical therapies must be considered to improve clinical outcomes of AMI-CAS.

Nonstandard Abbreviations and Acronyms

AMI-CAS	acute myocardial infarction complicating acute stroke
DAPT	dual-antiplatelet therapy
HBR	high bleeding risk
MACCE	major adverse cerebral/cardiovascular event

Acute myocardial infarction (AMI) infrequently occurs following acute stroke. Previous studies have reported that the occurrence of AMI was observed in 1.6% to 2.1% of patients with acute stroke, who exhibited an increased in-hospital mortality.[1–3] Primary percutaneous coronary intervention (PCI) and antithrombotic therapy with its appropriate potency are currently recommended to improve in-hospital and postdischarge cardiovascular outcomes in patients with AMI.[4,5] However, given that these therapies could elevate a risk of hemorrhagic stroke in the acute phase of stroke, appropriate management of ischemic and bleeding risks in patients with AMI complicating acute stroke (AMI-CAS) is challenging in the clinical settings.

Collaborative care with cardiologists and neurologists has a potential that enables selection of well-balanced therapeutic options for AMI-CAS.[6,7] Our institute has a structure to provide heart and brain team intensive care by cardiologists and neurologists for patients with cerebral and cardiovascular disease since 1977 (https://www.ncvc.go.jp/english/). This unique hospital feature provides an opportunity to investigate AMI-CAS with this specialized approach. Therefore, the current study investigated characteristics of therapeutic managements and ischemic and bleeding events in AMI-CAS through heart-brain team approach.

METHODS

Study Population

The current study retrospectively analyzed 2393 consecutive patients with AMI who were hospitalized at the National Cerebral and Cardiovascular Center (Suita, Japan) between January 1, 2007, and September 30, 2020 (Figure 1). Myocardial infarction was diagnosed according to the European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force for the Universal Definition of Myocardial Infarction.[7] Of these, takotsubo cardiomyopathy (n=3) was excluded. The remaining 2390 patients with AMI were included

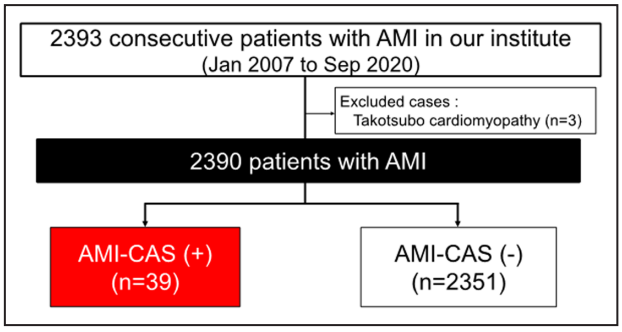

Figure 1. Patients' disposition.
The current study retrospectively analyzed 2393 consecutive patients with acute myocardial infarction (AMI) who were hospitalized at the National Cerebral and Cardiovascular Center (Suita, Japan) between January 1, 2007, and September 30, 2020. Of these patients, those with takotsubo cardiomyopathy (n=3) were excluded. The remaining 2390 patients with AMI were included in the current analysis. AMI-CAS indicates AMI complicating acute stroke.

in the current analysis (Figure 1). The research protocol was approved by the ethics committee of our institution (R21053). When we contacted participants by mail or telephone, we explained the study subjects and then obtained informed consent.

Definition of AMI-CAS

AMI-CAS was defined as the occurrence of AMI within 14 days after acute stroke. Acute stroke was defined as ischemic or hemorrhagic. Ischemic stroke causes included cardioembolic, atherosclerosis, and others. The timing of AMI occurrence after the onset of acute stroke was evaluated. The diagnosis of acute stroke was conducted by neurologists, according to the TOAST (trial of ORG 10172 in acute stroke treatment) criteria.[8]

Heart-Brain Team Approach of AMI-CAS

In patients with AMI-CAS, both cardiologist and neurologist discussed therapeutic management, including cardiac catheterization and antithrombotic therapies, according to status and severity of acute stroke and patient's condition.

Coronary Angiography and PCI

In those who presented with ST-segment–elevation myocardial infarction, the presence of hemorrhagic stroke and prognosis of acute stroke were evaluated first by computed tomography imaging and patient's symptomatic status. Emergent coronary angiography was conducted in patients who did not exhibit any hemorrhagic stroke but expected recovery from acute stroke. According to coronary angiographic features of culprit lesions and cause of acute stroke, PCI strategy was selected. Atherosclerotic lesion was mostly treated by stent implantation, whereas thrombectomy and/or balloon angioplasty were performed in patients with ST-segment–elevation myocardial infarction attributable to coronary embolism. In the case of in-stent restenosis or occlusion, balloon angioplasty was preferred.

In those with non–ST-segment–elevation myocardial infarction, coronary angiography was considered in patients exhibiting high- or very high-risk features[4,9] and expected recovery from acute stroke without hemorrhagic stroke. PCI was conducted in a similar manner as the aforementioned ST-segment–elevation myocardial infarction cases.

In both ST-segment–elevation myocardial infarction and non–ST-segment–elevation myocardial infarction cases with hemorrhagic stroke, conservative management was selected without any use of antithrombotic therapy or by using single antithrombotic therapy.

Antithrombotic Therapy

In patients who received stent implantation, loading of dual-antiplatelet therapy (DAPT) (200 mg aspirin+300 mg clopidogrel or 20 mg prasugrel) was conducted before primary PCI. DAPT with its approved maintenance dose in Japan (100 mg/d aspirin+75 mg/d clopidogrel or 3.75 mg/d prasugrel) was continued for at least 1 year after drug-eluting stent use or 1 month after bare metal stent use. In patients with atrial fibrillation, dual antithrombotic therapy (aspirin/clopidogrel+anticoagulation agent [vitamin K antagonist or direct oral anticoagulant]) or triple antithrombotic therapy (DAPT+anticoagulation agent) was commenced. In those treated by thrombectomy and/or balloon angioplasty, single antithrombotic therapy (aspirin, clopidogrel, or anticoagulation agent) was mostly selected.

Bleeding risk was evaluated by the Academic Research Consortium on high bleeding risk (HBR) and Japanese version of HBR criteria. Patients are considered to be HBR in subjects who fulfilled at least 1 major or 2 minor published HBR criteria.[10,11] With regard to Japanese version of HBR criteria, the Japanese Circulation Society has proposed it by considering additional clinical characteristics (low body weight, frailty, chronic kidney disease, heart failure, and peripheral vascular disease), which associate with bleeding events in Japanese patients.[12–14] By incorporating Academic Research Consortium HBR major/minor criteria and these ones, HBR in Japanese patients is defined as at least 1 major or 2 minor Japanese version of HBR criteria.[15]

Outcomes

The primary outcome was defined as a composite of major adverse cerebral/cardiovascular events (MACCEs), which included cardiac-cause death, nonfatal myocardial infarction, and nonfatal stroke. The secondary outcome was defined as major bleeding events that corresponded to Bleeding Academic Research Consortium 3 or 5.[8] These outcomes were first obtained through reviewing the medical records. If needed, questionnaire was conducted by mail or telephone follow-up. A clinical event committee consisting of physicians (T.S. and Y.K.) with another referee (M.F.) in case of disagreement adjudicated all events on the basis of the aforementioned original source documents of outcomes. T.S. and Y.K. had full access to all the data in the study and take responsibility for their integrity and the data analysis.

Statistical Analysis

Continuous variables were expressed as the mean±SD and compared using the *t* test if data were normally distributed. When variables were not normally distributed, their results are expressed as median (interquartile

range) using the Mann-Whitney *U* test. Categorical variables were compared using the Fisher exact test or the χ^2 test, as appropriate. The Kaplan-Meier method was used to estimate survival curves for primary and secondary outcomes, and log-rank test was used to assess differences between patients with AMI with and without acute stroke. Unadjusted hazard ratios (HRs) for MACCEs and major bleeding were calculated with univariable Cox proportional hazards model. Adjusted HRs were calculated by multivariable Cox proportional hazards model with $P<0.20$. All analyses were performed using SPSS version 28 (IBM, Armonk, NY), R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria), and MatchIt version 4.3.0.

Data Availability Statement

The data sharing underlying this article requires the approval of principal investigator and the research ethics committee at National Cerebral and Cardiovascular Center.

RESULTS

Clinical Characteristics of AMI-CAS

In the current study, AMI-CAS was identified in 1.6% (39/2390) of study subjects. Clinical demographics of patients with AMI-CAS are shown in Table 1. They were more likely to be women (46.2% versus 26.2%; $P=0.005$) and have a history of chronic kidney disease (71.8% versus 47.0%; $P=0.002$), atrial fibrillation (38.5% versus 9.8%; $P<0.001$), and stroke (33.3% versus 11.1%; $P<0.001$). They were less likely to be current smokers (25.6% versus 43.5%; $P=0.03$). In addition, a lower hemoglobin (12.5 [19.6–24.4] versus 13.6 [12.2–14.9] g/dL; $P=0.03$) level with smaller peak creatine kinase (781 [370–1912] versus 1486 [651–3056] IU/L; $P=0.008$) and creatine kinase MB (69 [19.5–207] versus 149 [57–314] IU/L; $P=0.004$) levels was observed in AMI-CAS.

With regard to characteristics of acute stroke, 37 patients (37/39=94.9%) were diagnosed as having ischemic stroke, and 2 patients presented with hemorrhagic stroke. Of these patients, 69.2% and 10.3% of them were attributable to cardioembolic and atherosclerotic causes, respectively (Table 1). Median duration of AMI from the onset of acute stroke was 2 days (interquartile range, 0–8 days). AMI occurred within 3 days from the onset of acute stroke in 59.0% of patients with AMI-CAS.

Coronary Revascularization and Antithrombotic and Other Medical Therapies

Table 2 summarizes coronary angiography and PCI procedures. The frequency of emergent coronary angiography was significantly lower in patients with AMI-CAS (59.0% versus 93.2%; $P<0.001$) (Table 2). Primary PCI was conducted in only 43.6% of them, which was significantly lower compared with those without acute stroke (43.6% versus 84.7%; $P<0.001$) (Table 2). Analyses of PCI procedural characteristics demonstrated that a proportion of thrombectomy was higher in patients with AMI-CAS (7.7% versus 1.4%; $P=0.02$), whereas they less frequently received stent implantation (30.8% versus 77.9%; $P<0.001$). There were no significant differences in the proportion of mechanical circulatory support (15.4% versus 16.6%; $P=0.84$) between 2 groups (Table 2). Coronary angiographic features of 2214 subjects with AMI (acute stroke [+]: n=23; acute stroke [–]: n=2191) are shown in Table S1. Culprit lesions in patients with AMI-CAS were less likely to be located at the proximal segment of major coronary arteries (21.7% versus 42.7%; $P=0.04$). The proportion of multivessel disease was similar between 2 groups (65.2% versus 56.1%; $P=0.38$) (Table S1).

Table 3 describes the use of antithrombotic and other medical therapies. Dual-antithrombotic therapy was less frequently used in patients with AMI-CAS, and 33.3% of them did not receive any antithrombotic agents. Regimen of dual-antithrombotic therapy in patients with AMI-CAS was characterized as a less frequent use of DAPT (38.5% versus 85.7%), especially a combination of aspirin and prasugrel (2.6% versus 24.5%), whereas there was no significant difference in the regimen of triple antithrombotic therapy ($P=1.00$). The use of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (59.0% versus 77.8%; $P=0.005$) and statin (48.7% versus 82.3%; $P<0.001$) was significantly lower in patients with AMI-CAS (Table 3).

Cardiovascular and Major Bleeding Outcomes of Patients With AMI-CAS

In the current study, there were 331 MACCEs and 109 major bleeding events during the observational period (median, 2.4 years [interquartile range, 1.1–4.4 years]) (Table S2). AMI-CAS was associated with a 3.47- and 3.30-fold greater likelihood of experiencing MACCEs (95% CI, 1.99–6.05; $P<0.001$) and major bleeding events (95% CI, 1.34–8.10; $P=0.009$), respectively (Tables 4 and 5 and Figures 2 and 3). Multivariable-adjusted models still continued to demonstrate AMI-CAS as an independent predictor for the occurrence of MACCEs (HR, 1.87 [95% CI, 1.02–3.42]; $P=0.04$) and major bleeding events (HR, 2.67 [95% CI, 1.03–6.93]; $P=0.04$) (Tables 4 and 5). Figure S1 illustrated comparison of each component of MACCE between 2 groups. Patients with AMI-CAS exhibited an increased risk of nonfatal stroke (HR, 6.48 [95% CI, 3.15–13.3]; $P<0.001$) but not cardiac-cause death (HR, 2.21 [95% CI, 0.91–5.28]; $P=0.08$) and nonfatal myocardial infarction (HR, 1.29 [95% CI, 0.18–9.31]; $P=0.80$) (Figure S1). Detailed

Table 1. Clinical Demographics

Characteristic	AMI-CAS (+) (n=39)	AMI-CAS (–) (n=2351)	*P* value
Age, y*	73 (67–83)	72 (62–79)	0.21
Female sex, n (%)	18 (46.2)	617 (26.2)	0.005
Hypertension, n (%)	31 (79.5)	1664 (70.8)	0.24
Dyslipidemia, n (%)	22 (56.4)	1612 (68.6)	0.11
Diabetes, n (%)	17 (43.6)	877 (37.3)	0.42
Current smoking, n (%)	10 (25.6)	1022 (43.5)	0.03
Body mass index, kg/m^2*	22.7 (19.6–24.4)	23.4 (21.2–25.7)	0.06
Hemoglobin, g/dL*	12.5 (11.3–14.2)	13.6 (12.2–14.9)	0.03
CKD, n (%)	28 (71.8)	1106 (47.0)	0.002
Hemodialysis, n (%)	4 (10.3)	86 (3.7)	0.06
History of atrial fibrillation, n (%)	15 (38.5)	231 (9.8)	<0.001
History of myocardial infarction, n (%)	3 (7.7)	251 (10.7)	0.80
History of stroke, n (%)	13 (33.3)	260 (11.1)	<0.001
HBR measures, n (%)			
ARC-HBR	39 (100)	1150 (48.9)	<0.001
Japanese version of HBR criteria	39 (100)	1378 (58.6)	<0.001
Clinical presentation of AMI			
STEMI, n (%)	24 (61.5)	1731 (73.6)	0.09
NSTEMI, n (%)	15 (38.5)	619 (26.3)	
Killip class ≥2, n (%)	11 (28.2)	507 (21.6)	0.32
LVEF, %*	44 (34–56)	49 (41–57)	0.09
Peak CK, IU/L*	781 (370–1912)	1486 (651–3056)	0.008
Peak CK-MB, IU/L*	69 (19–207)	149 (57–314)	0.004
Characteristics of acute stroke, n (%)			
Ischemic	37 (94.9)	…	…
Cardioembolic	27 (69.2)	…	…
Atherosclerotic	4 (10.3)	…	…
Others	6 (15.4)	…	…
Hemorrhagic	2 (5.1)	…	…
Treatment for acute stroke, n (%)			
Antithrombotic therapy alone	33 (84.6)	…	…
Intravenous thrombolysis	3 (7.7)	…	…
Endovascular treatment	4 (10.3)	…	…
Duration of AMI from the onset of acute stroke			
Median duration, d	2.0 (0–8)	…	…
0–3 d, n (%)	23 (59.0)	…	…
4–7 d, n (%)	7 (17.9)	…	…
8–14 d, n (%)	9 (23.1)	…	…

AMI indicates acute myocardial infarction; AMI-CAS, AMI complicating acute stroke; ARC-HBR, Academic Research Consortium for HBR; CK, creatine kinase; CKD, chronic kidney disease; HBR, high bleeding risk; LVEF, left ventricular ejection fraction; NSTEMI, non–ST-segment–elevation myocardial infarction; and STEMI, ST-segment–elevation myocardial infarction.

*Values expressed as the median (interquartile range).

clinical demographics in patients with AMI-CAS are shown in Table S3.

DISCUSSION

Poststroke cardiovascular complications have been reported to associate with an elevated risk of their outcomes, which underscore heart and brain team approach. In the current study, under intensive management with both cardiologists and neurologists, patients with AMI-CAS still less likely received guideline-recommended primary PCI and DAPT. During the 2.4-year observational period, a greater frequency of MACCEs and major bleeding events was observed in patients with AMI-CAS. These observations indicate

Table 2. Coronary Angiography and PCI Procedures

Variable	AMI-CAS (+) (n=39)	AMI-CAS (–) (n=2351)	*P* value
Emergent coronary angiography	23 (59.0)	2191 (93.2)	<0.001
Primary PCI	17 (43.6)	1992 (84.7)	<0.001
Balloon angioplasty	2 (5.1)	82 (3.5)	0.65
Thrombectomy	3 (7.7)	33 (1.4)	0.02
Stent implantation	12 (30.8)	1832 (77.9)	<0.001
BMS	4 (10.3)	689 (29.3)	<0.001
DES	8 (20.5)	1143 (48.6)	
Mechanical support	6 (15.4)	390 (16.6)	0.84

Data are given as number (percentage). AMI-CAS indicates acute myocardial infarction complicating acute stroke; BMS, bare metal stent; DES, drug-eluting stent; and PCI, percutaneous coronary intervention.

AMI-CAS as a substantially high-risk subject with challenging features to select coronary revascularization and antithrombotic therapies.

An elevated risk of MACCEs, especially cardiac-cause death and nonfatal stroke, in patients with AMI-CAS could be explained by the brain and heart interactions. Pathophysiologically, poststroke neuronal death induces local inflammation, including interleukin-1.[16–18] Interleukin-1 and inflammatory cells activate macrophages, which cause atherogenesis, endothelial dysfunction, and plaque rupture.[19] Moreover, stroke is associated with systematic release of catecholamines, which is driven by sympathetic stimulation of the adrenal glands and the effect of inflammation on hypothalamic-pituitary adrenal axis.[16,20–22] These stroke-related inflammatory and autonomic mechanisms may result in the occurrence of AMI after acute stroke and subsequent cardiovascular events observed in the current analysis. Propagation of atherosclerosis into polyvascular territories worsens cardiovascular outcomes.[23] A recent study reported a stepwise increased cardiovascular risk in association with the number of affected vascular beds.[24] Given that polyvascular disease has been shown to exhibit a greater inflammatory activity, including interleukin-6 and high-sensitivity CRP (C-reactive protein),[25] these inflamed disease substrates may also exist in AMI-CAS, which ultimately causes future cardiovascular events. The concomitance of chronic kidney disease, atrial fibrillation, and a history of stroke could be additional cardiovascular risk enhancers in AMI-CAS.[26,27] The inflammatory and autonomic changes after stroke with a clustering of atherogenic risks indicate the need for more intensified management of cardiovascular risk

Table 3. Antithrombotic and Other Medical Therapy

Variable	AMI-CAS (+) (n=39)	AMI-CAS (–) (n=2351)	*P* value
Antithrombotic therapy			
SAPT	5 (12.8)	161 (6.8)	0.19
DAT	18 (46.2)	2055 (87.4)	<0.001
TAT	1 (2.6)	99 (4.2)	1.00
No use of any antithrombotic agents	13 (33.3)	31 (1.3)	<0.001
Regimen of DAT			
DAPT	15 (38.5)	2015 (85.7)	<0.001
Aspirin+clopidogrel	11 (28.2)	1027 (43.7)	0.053
Aspirin+prasugrel	1 (2.6)	576 (24.5)	0.001
Clopidogrel+DOAC	1 (2.6)	1 (0.04)	0.03
Regimen of TAT, n (%)			
DAPT+warfarin	0 (0)	62 (2.6)	0.62
DAPT+DOAC	1 (2.6)	37 (1.6)	0.47
Other medical therapy			
ACEI/ARB	23 (59.0)	1829 (77.8)	0.005
β-Blocker	21 (53.8)	1588 (67.5)	0.07
Statin	19 (48.7)	1936 (82.3)	<0.001

Data are given as number (percentage). ACEI indicates angiotensin-converting enzyme inhibitor; AMI-CAS, acute myocardial infarction complicating acute stroke; ARB, angiotensin II receptor blocker; DAPT, dual-antiplatelet therapy; DAT, dual-antithrombotic therapy; DOAC, direct oral anticoagulant; SAPT, single-antiplatelet therapy; and TAT, triple antithrombotic therapy.

Table 4. Univariate and Multivariate Analyses of Predictors for MACCEs

	Univariate analysis			Multivariate analysis		
Variable	Hazard ratio (95% CI)	*P* value	*P* value for Schoenfeld residual test	Hazard ratio (95% CI)	*P* value	*P* value for Schoenfeld residual test
AMI-CAS	3.47 (1.99–6.05)	<0.001	0.81	2.14 (1.02–4.48)	0.043	0.220
Female sex	0.85 (0.67–1.08)	0.18	0.19	…	…	…
Age	1.03 (1.02–1.04)	<0.001	0.41	…	…	…
BMI	0.96 (0.93–0.99)	0.03	0.12	…	…	…
Hypertension	1.35 (1.05–1.73)	0.02	0.01	1.08 (0.95–1.24)	0.224	0.942
Dyslipidemia	0.77 (0.62–0.97)	0.02	0.34	…	…	…
Diabetes	1.27 (1.03–1.58)	0.03	0.16	…	…	…
CKD	2.89 (2.30–3.64)	<0.001	0.02	1.10 (0.99–1.22)	0.075	0.72
Hemodialysis	2.98 (2.05–4.34)	<0.001	0.79	…	…	…
Atrial fibrillation	1.99 (1.50–2.64)	<0.001	0.91	…	…	…
Killip class ≥2	4.72 (3.80–5.85)	<0.001	<0.001	1.05 (0.94–1.17)	0.351	0.596
LVEF <30%	5.70 (4.46–7.29)	<0.001	0.001	1.30 (1.10–1.53)	0.002	0.026
Emergent PCI	0.53 (0.41–0.69)	<0.001	0.63	…	…	…
DAPT	0.44 (0.34–0.58)	<0.001	0.1	…	…	…
Statin	0.23 (0.19–0.29)	<0.001	<0.001	0.89 (0.79–0.99)	0.036	0.071
ACEI/ARB	0.23 (0.18–0.28)	<0.001	<0.001	0.92 (0.82–1.04)	0.184	0.306
β Blocker	0.35 (0.28–0.44)	<0.001	<0.001	1.03 (0.92–1.15)	0.605	0.085

ACEI indicates angiotensin-converting enzyme inhibitor; AMI-CAS, acute myocardial infarction complicating acute stroke; ARB, angiotensin II receptor blocker; BMI, body mass index; CKD, chronic kidney disease; DAPT, dual-antiplatelet therapy; LVEF, left ventricular ejection fraction; MACCE, major adverse cerebral/cardiovascular event; and PCI, percutaneous coronary intervention.

factors, inflammation, and adrenergic response in patients with AMI-CAS.

A significantly lower frequency of primary PCI, DAPT, and other established antiatherosclerotic medical therapies may also account for their worse cardiovascular outcomes. The analysis of the national inpatient sample in the United States reported that only 2% of patients with AMI complicating acute ischemic strokes received PCI, which was associated with a lower in-hospital mortality.[2] In the current study, both cardiologists and neurologists had sharded decision making, according to disease condition of AMI and acute stroke. As a consequence, a numerically greater proportion of patients with AMI-CAS received primary PCI (43.5%). However, the remaining 54.7% of them were not still optimally revascularized. In addition, the frequency of DAPT use was only 38.5%, and 33.3% of patients with AMI-CAS did not receive any antithrombotic agents, despite their elevated ischemic risks. As such, difficulties exist in conducting guideline-recommended coronary revascularization and antithrombotic therapy in a substantial proportion of patients with AMI-CAS, which could result in failure to mitigate future cardiovascular event risks after AMI.

We observed a lower frequency use of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, β-blocker, and statin in subjects with AMI-CAS. They more likely exhibited a history of chronic kidney disease with a trend toward lower left ventricular ejection fraction. These features may make it difficult to commence renin-angiotensin inhibitors and β blockades. In the current study, 69.2% (27/39) of patients with AMI-CAS exhibited a high modified Rankin Scale score (≥4). Given that this condition could cause eating and swallowing disability, this may negatively affect physician's decision to commence a statin in patients with AMI-CAS. Further improvement of awareness to use established medications is needed to achieve better cardiovascular outcomes in subjects with AMI-CAS.

Major bleeding has important implications associated with prognosis.[28] In the current analysis, major bleeding event risk was elevated in patients with AMI-CAS, despite a lower frequency of dual-antithrombotic therapy and DAPT use.[29,30] Mechanistically, one would expect that bleeding risk may be derived by their concomitant HBR features, including female sex and anemia.[31,32] Recent studies have shown a potential link of ischemic and bleeding events with biomarkers, such as growth differentiation factor-15, in the setting of acute coronary syndrome and acute stroke.[33,34] Given the effect of this stress-responsive cytokine to inhibit integrin activation on platelets, it could be argued that AMI-CAS may harbor more activated cytokine secretion, including growth differentiation factor-15, which could induce not only ischemic but bleeding events.

Table 5. Univariate and Multivariate Analyses of Predictors for Major Bleeding Events

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio (95% CI)	*P* value	*P* value for Schoenfeld residual test	Hazard ratio (95% CI)	*P* value	*P* value for Schoenfeld residual test
AMI-CAS	3.30 (1.34–8.10)	0.009	0.049	1.64 (1.01–2.65)	0.044	0.3
Female sex	0.54 (0.37–0.79)	0.002	0.15	…	…	…
Age	1.05 (1.03–1.07)	<0.001	0.26	…	…	…
BMI	0.93 (0.88–0.99)	0.011	0.57	…	…	…
Hypertension	0.94 (0.63–1.42)	0.79	0.27	…	…	…
Dyslipidemia	0.71 (0.49–1.05)	0.087	0.56	…	…	…
Diabetes	0.82 (0.55–1.22)	0.32	0.37	…	…	…
Atrial fibrillation	1.45 (0.84–2.50)	0.18	0.51	…	…	…
CKD	2.57 (1.72–3.85)	<0.001	0.83	…	…	…
Hemodialysis	1.31 (0.53–3.21)	0.56	0.042	…	…	…
Hemoglobin	0.83 (0.76–0.90)	<0.001	0.095	…	…	…
Killip class ≥2	4.74 (3.25–6.91)	<0.001	0.002	0.97 (0.70–1.36)	0.8763	0.25
LVEF <30%	4.90 (3.21–7.48)	<0.001	0.24	…	…	…
Emergent PCI	0.56 (0.36–0.87)	0.009	0.46	…	…	…
DAPT	0.57 (0.34–0.94)	0.03	0.71	…	…	…
TAT	1.66 (0.77–3.57)	0.19	0.16	…	…	…

AMI-CAS indicates acute myocardial infarction complicating acute stroke; BMI, body mass index; CKD, chronic kidney disease; DAPT, dual-antiplatelet therapy; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; and TAT, triple antithrombotic therapy.

A smaller creatine kinase level was observed in subjects with AMI-CAS. On coronary angiographic analysis, although initial TIMI (Thrombolysis in Myocardial Infarction) trial grade flow did not differ between 2 groups, culprit lesion in subjects with AMI-CAS was less frequently located at the proximal coronary segment (Table S1). This angiographical characteristic could account for their smaller creatine kinase levels.

The advantage of heart-brain team is to optimize therapeutic management in patients with AMI-CAS. Risks and benefits of invasive strategy could differ in each individual, according to disease severity/

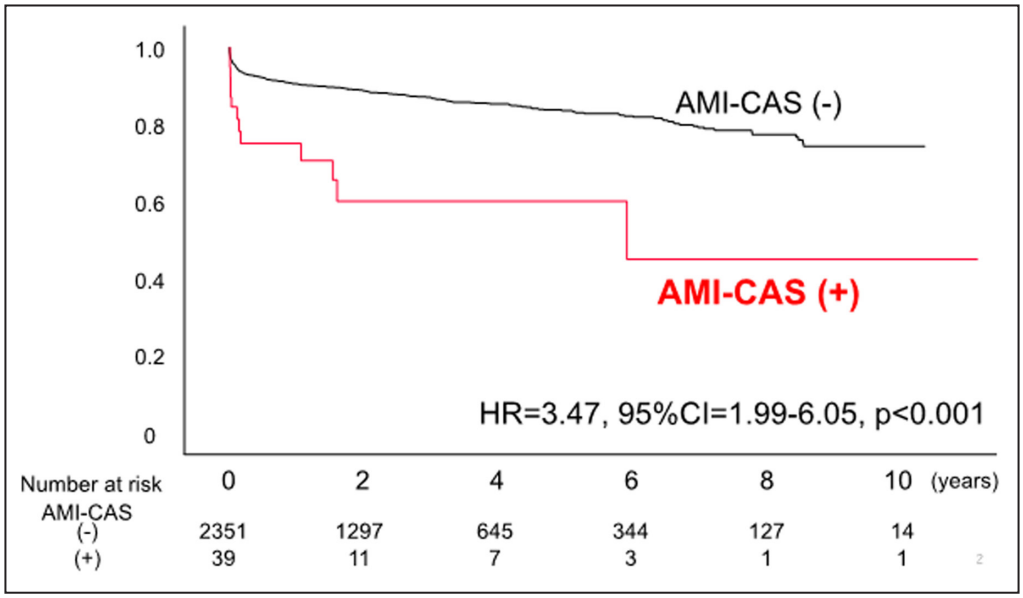

Figure 2. Comparison of major adverse cerebral/cardiovascular events (MACCEs).
During the observational period (median, 2.4 years), acute myocardial infarction complicating acute stroke (AMI-CAS) was associated with a 3.47-fold greater likelihood experiencing MACCEs (95% CI, 1.99–6.05; *P*<0.001). HR indicates hazard ratio.

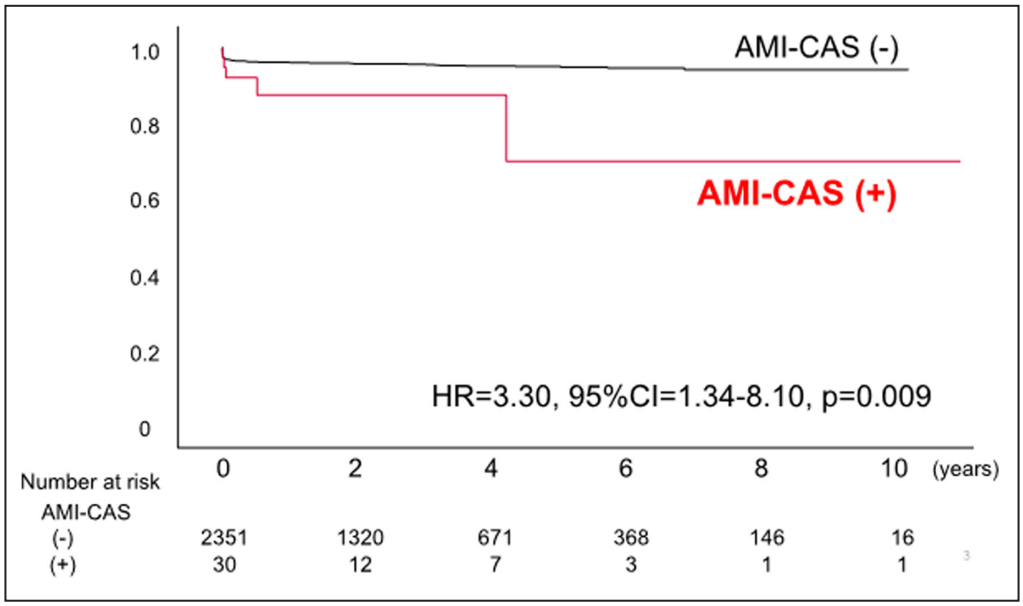

Figure 3. Comparison of major bleeding events.
A 3.30-fold greater risk of major bleeding events was observed in patients with acute myocardial infarction complicating acute stroke (AMI-CAS) (95% CI, 1.34–8.10; *P*=0.009). HR indicates hazard ratio.

prognosis, risks of cardiac catheterization, and applicability of antithrombotic therapies. Heart-brain team approach enables cardiologists and neurologists to share understanding of these disease-related characteristics.[7] Then, the team could determine appropriate strategy (invasive, delayed invasive, or noninvasive strategies) throughout interactive discussion (Figure 4).

As mentioned above, several hurdles exist in terms of coronary revascularization and antithrombotic therapy. Novel antithrombotic agents with well-balanced

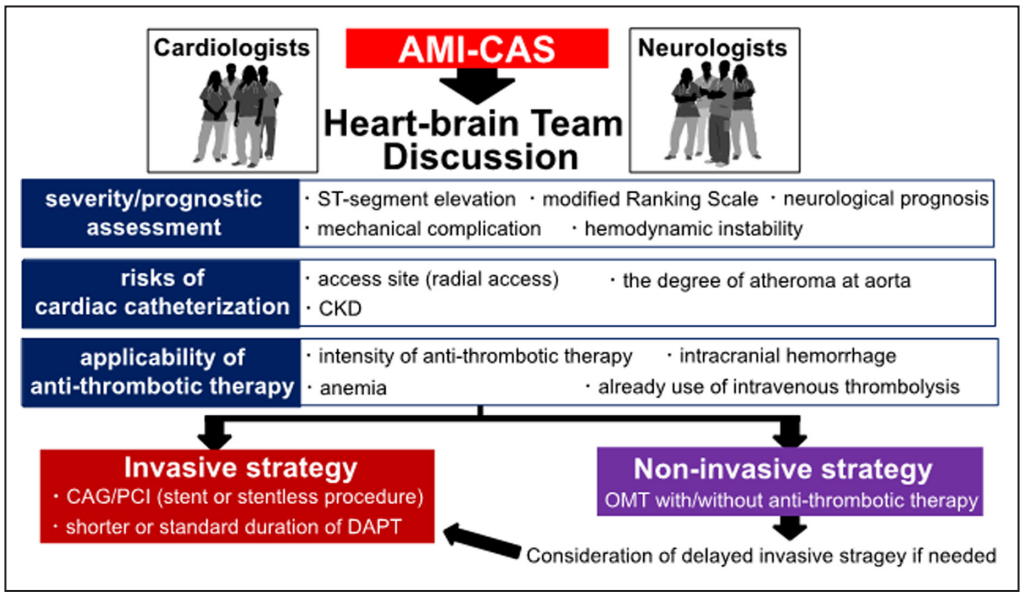

Figure 4. Heart-brain team management of acute myocardial infarction complicating acute stroke (AMI-CAS).
In patients with AMI-CAS, heart-brain team approach enables both cardiologists and neurologists to discuss disease severity/prognosis, risks of cardiac catheterization, and applicability of antithrombotic therapies. This approach helps to optimize therapeutic management of AMI-CAS (invasive, delayed invasive, or noninvasive strategy). CAG indicates coronary angiography; CKD, chronic kidney disease; DAPT, dual-antiplatelet therapy; OMT, optimal medical therapy; and PCI, percutaneous coronary intervention.

efficacies to reduce both ischemic and bleeding risks are expected to further improve outcomes in patients with AMI-CAS. A recent clinical trial has reported the superiority of DAPT, with its short duration after drug-eluting stent implantation, in patients with acute coronary syndrome.[35] This antithrombotic regimen may be more suitable in patients with AMI-CAS. The awareness toward the benefit of lipid-lowering therapies as well as other established medical therapies should be further improved in the setting of poststroke cardiovascular complications. Given the relationship of stroke-related inflammation with cardiovascular complications, anti-inflammatory therapies may be effective in modulating cardiovascular risks of AMI with acute stroke.[19,36] Recent clinical trials have demonstrated a reduction of cardiovascular events with modulating inflammatory activities.[19] Further investigation is warranted to elucidate the effect of targeting inflammation on poststroke cardiovascular diseases.

Study Limitations

Several caveats should be considered to interpret the current findings. First, this is a retrospective, single-center, observational study, which included relatively small numbers of patients with AMI-CAS. Despite these limitations, a multivariable Cox proportional hazards model consistently showed a significant relationship between AMI-CAS and MACCEs and major bleeding. Second, the current study analyzed subjects with AMI from 2007 to 2020. During this period, guidelines for coronary revascularization and antithrombotic and lipid-lowering therapies have changed, which may affect cardiovascular and bleeding outcomes in the study subjects. Third, the current study analyzed outcomes of patients with AMI-CAS treated by both cardiologists and neurologists. Their outcomes may be different at centers that do not have a heart-brain team. Given that our institute has had both heart and brain intensive care units since 1977, we do not have any data about conventionally managed patients with AMI-CAS. Therefore, the current study does not compare the efficacy of heart-brain team approach with conventional one. Further dedicated study is required to evaluate whether heart-brain team approach is effective to manage patients with AMI-CAS. Fourth, the selection of guideline-recommended invasive management and medical therapy was conducted according to each physician's discretion, which may be susceptible to selection bias. Fifth, the current study included Japanese subjects only. Because ethnic-related difference exists in the frequency of obstructive and hemorrhagic stroke, therapeutic management and cardiovascular outcomes may be different in non-Japanese patients with AMI-CAS. Last, the current study did not measure any biomarkers that reflect inflammatory activity associated with AMI and acute stroke.

CONCLUSIONS

In conclusion, AMI-CAS was observed in 1.6% of subjects with AMI. Under heart-brain team approach, they were less likely to receive guideline-recommended coronary revascularization and medical therapy. Furthermore, a substantially elevated risk of cardiovascular and major bleeding events was observed in the setting of AMI-CAS. The current findings indicate that difficulties still exist in conducting coronary revascularization and antithrombotic therapy in patients with AMI-CAS receiving heart-brain intensive care. Further studies are required to search more refined management of AMI-CAS.

ARTICLE INFORMATION

Received June 17, 2022; accepted December 13, 2022.

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Acknowledgments

We would like to acknowledge cardiology medical fellows and Miss Yuko Yoshioka for their excellent assistance.

Sources of Funding

None.

Disclosures

Dr Kataoka has received research support from Nipro and Abbott; and honoraria from Nipro, Abbott, Kowa, Amgen, Sanofi, Astellas, Takeda, and Daiichi-Sankyo. Dr Toyoda received honoraria from Daiichi-Sankyo, Otsuka, Novartis, Bayer, Bristol-Myers Squibb, and Abbott Medical, outside the submitted work. Other authors have nothing to disclose.

Supplemental Material

Tables S1–S3
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Location of culprit lesion

	AMI receiving coronary angiography (n=2214)		p value
	AMI-CAS (+) (n=23)	AMI-CAS (-) (n=2191)	
LMT, n (%)	1 (4.3)	87 (4.0)	0.87
LAD, n (%)	9 (39.1)	810 (37.0)	
LCX, n (%)	1 (4.3)	247 (11.3)	
RCA, n (%)	9 (39.1)	827 (37.7)	
Proximal segment, n (%) *	5 (21.7)	936 (42.7)	0.04
Multivessel disease, n (%)	15 (65.2)	1229 (56.1)	0.38
Initial TIMI Grade Flow			
Grade 0, n (%)	998 (46.8)	8 (34.8)	0.48
Grade 1, n (%)	126 (5.9)	1 (4.3)	
Grade 2, n (%)	538 (25.2)	6 (26.1)	
Grade 3, n (%)	471 (22.1)	8 (34.8)	

*Proximal lesion defined less than 20mm from each ostium.

AMI-CAS = acute myocardial infarction complicating acute stroke, CAG = coronary artery angiography, LAD = left anterior descending artery, LCX = left circumflex artery, LMT = left main trunk, TIMI = thrombolysis in myocardial infarction

Table S2. Summary of MACCE and Major Bleeding

	Overall (n=2390)	AMI-CAS (+) (n=39)	AMI-CAS (-) (n=2351)
MACCE (= cardiac-cause death, non-fatal MI, non-fatal stroke), n (%)	331 (13.8)	13 (33.3)	318 (13.5)
Cardiac-cause death, n (%)	179 (7.5)	5 (12.8)	174 (7.4)
Non-fatal MI, n (%)	72 (3.0)	1 (2.6)	71 (3.0)
Non-fatal stroke, n (%)	116 (4.9)	8 (20.5)	108 (4.6)
Major bleeding, n (%)	109 (4.6)	5 (12.8)	104 (4.4)

AMI-CAS = acute myocardial infarction complicating acute stroke, MACCE = major adverse cardiac and cerebrovascular events, MI = myocardial infarction.

Table S3. Detailed Clinical Demographics in AMI Patients Complicating Acute Stroke

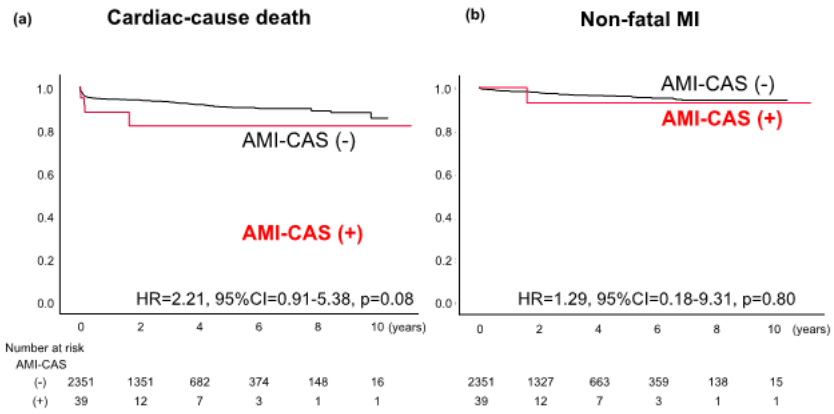
	Age/ sex	STEMI/ NSTEMI	Stroke etiology	Timing	Hemodynamic instability	PCI	Anti-thrombotic agents	mRS	MACCE	Major Bleeding
1	72/M	STEMI	Embolic	day 0	-	BMS	DAPT	5	Stroke	-
2	67/M	STEMI	Hemorrhagic	day 13	-	-	None	5	Stroke	-
3	71/M	STEMI	Other	day 0	+	BMS	DAPT	6	CV death	-
4	86/M	STEMI	Embolic	day 0	+	-	None	6	CV death	-
5	62/F	STEMI	Atherosclerotic	day 0	-	BMS	DAPT	1	-	-
6	49/M	STEMI	Embolic	day 2	+	Thrombectomy	None	2	-	-
7	84/M	STEMI	Embolic	day 2	-	-	DOAC+P2Yi	2	-	-
8	86/M	STEMI	Embolic	day 4	-	-	None	4	-	-
9	64/M	STEMI	Embolic	day 9	+	-	DOAC+P2Yi	2	Stroke	-
10	64/F	STEMI	Embolic	day 0	-	Thrombectomy	OAC	1	MI	-
11	59/M	STEMI	Embolic	day 0	-	-	SAPT	4	-	-
12	88/M	STEMI	Embolic	day 2	-	DES	DAPT	1	-	-
13	73/F	STEMI	Embolic	day 0	-	-	SAPT	6	CV death	-
14	74/F	STEMI	Other	day 3	+	DES	DAPT	6	CV death	GIB
15	74/F	STEMI	Other	day 7	+	DES	DAPT	1	-	-
16	91/F	STEMI	Hemorrhagic	day 2	-	-	None	5	-	-
17	72/F	STEMI	Embolic	day 0	+	DES	DAPT	3	Stroke	-
18	73/F	STEMI	Embolic	day 0	-	-	None	2	-	-
19	84/F	STEMI	Embolic	day 6	-	-	None	5	-	-
20	72/M	STEMI	Embolic	day 0	-	Thrombectomy	TAT	4	Stroke	-
21	53/M	STEMI	Embolic	day 1	+	DES	DAPT	5	-	Intracranial hemorrhage
22	73/F	STEMI	Other	day 1	-	DES	DAPT	3	-	GIB
23	81/F	STEMI	Embolic	day 5	-	-	None	5	-	-
24	73/M	STEMI	Embolic	day 13	-	-	None	5	-	hematoma
25	76/F	NSTEMI	Embolic	day 4	+	-	SAPT	4	-	-
26	69/M	NSTEMI	Other	day 5	-	-	SAPT	4	-	GIB

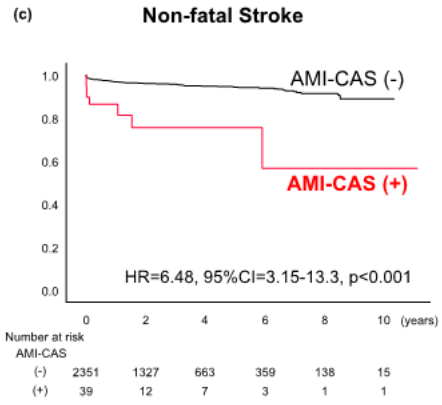
27	65/M	NSTEMI	Embolic	day 2	-	BMS	DAPT	4	Stroke	-
28	71/M	NSTEMI	Atherosclerotic	day 1	-	CABG	DAPT	4	-	-
29	76/F	NSTEMI	Embolic	day 0	+	-	None	5	-	-
30	67/M	NSTEMI	Embolic	day 14	-	-	None	5	-	-
31	87/F	NSTEMI	Embolic	day 9	-	-	OAC	4	-	-
32	74/M	NSTEMI	Embolic	day 6	-	-	None	4	-	-
33	65/M	NSTEMI	Atherosclerotic	day 8	-	POBA	DAPT	2	-	-
34	68/F	NSTEMI	Embolic	day 0	-	DES	DAPT	4	Stroke	-
35	93/F	NSTEMI	Embolic	day 9	+	-	DAPT	5	Stroke	-
36	85/F	NSTEMI	Atherosclerotic	day 8	-	-	DOAC+P2Yi	4	-	-
37	93/F	NSTEMI	Embolic	day 1	-	-	None	5	-	-
38	71/M	NSTEMI	Other	day 0	+	POBA	SAPT	5	-	-
39	49/M	NSTEMI	Embolic	day 10	-	DES	DAPT	1	-	-

AMI = acute myocardial infarction, BMS = bare metal stent, CABG = coronary artery bypass grafting, CV death = cardiovascular death, DAPT = dual anti-platelet therapy, DES = drug-eluting stent, DOAC = direct oral anticoagulant, GIB = gastrointestinal bleeding, MI = myocardial infarction, mRS = modified Rankin Scale, NSTEMI = non-ST-segment elevation myocardial infarction, OAC = oral anticoagulant, PCI = percutaneous coronary intervention, POBA = plain old balloon angioplasty, P2Y12I = P2Y12 inhibitor, SAPT = single anti-platelet therapy, STEMI = ST-segment elevation myocardial infarction, TAT = triple anti-thrombotic therapy

Figure S1. Comparison of Cardiac-cause Death, Non-fatal MI and Non-fatal Stroke

(a) Cardiac-cause death, **(b)** Non-fatal MI, **(c)** Non-fatal stroke





AMI-CAS exhibited an increased risk of non-fatal stroke (HR 6.48, 95%CI= 3.15-13.3, p<0.001) but not cardiac-cause death (HR 2.21, 95%CI=0.91-5.28, p=0.08) and non-fatal MI (HR 1.29, 95%CI=0.18-9.31, p=0.80).

AMI = acute myocardial infarction, AMI-CAS = acute myocardial infarction complicating acute stroke, CI = confidence interval, HR = hazard ratio, MI = myocardial infarction, MACCE = major adverse cerebral and cardiovascular events