Circulation Reports
Circ Rep 2021; 3: 267–272
doi:10.1253/circrep.CR-21-0010

ORIGINAL ARTICLE
Ischemic Heart Disease

Impact of Prior Stroke on Long-Term Outcomes in Patients With Acute Coronary Syndrome

Mitsuhiro Takeuchi, MD; Hideki Wada, MD, PhD; Manabu Ogita, MD, PhD; Daigo Takahashi, MD; Yui Okada-Nozaki, MD; Ryota Nishio, MD; Kentaro Yasuda, MD; Norihito Takahashi, MD; Taketo Sonoda, MD; Shoichiro Yatsu, MD, PhD; Jun Shitara, MD, PhD; Shuta Tsuboi, MD, PhD; Tomotaka Dohi, MD, PhD; Satoru Suwa, MD; Katsumi Miyauchi, MD; Hiroyuki Daida, MD; Tohru Minamino, MD, PhD

Background: Cerebrovascular disease often coexists with coronary artery disease (CAD), and it has been associated with worse clinical outcomes in CAD patients. However, the prognostic effect of prior stroke on long-term outcomes in patients with acute coronary syndrome (ACS) is still unclear.

Methods and Results: An observational cohort study of ACS patients who underwent emergency percutaneous coronary intervention (PCI) between January 1999 and May 2015 was conducted. Patients were divided into 2 groups according to their history of stroke. We evaluated both all-cause death and cardiac death. Of the 2,548 consecutive ACS patients in the current cohort, 268 (10.5%) had a history of stroke at the onset of ACS. Patients with a history of stroke were older and had a higher prevalence of comorbidities such as hypertension or renal deficiency. The cumulative incidences of all-cause death and cardiac death were significantly higher in patients with a history of stroke (both log-rank P<0.0001). Multivariate Cox hazard regression analysis showed that a history of stroke was significantly associated with the incidences of all-cause death (hazard ratio [HR] 1.49, 95% confidence interval [CI] 1.20–1.85, P=0.0004) and cardiac death (HR 1.41, 95% CI 1.03–1.93, P=0.03).

Conclusions: About 10% of the ACS patients had a history of stroke and had worse clinical outcomes.

Key Words: Coronary artery disease; Percutaneous coronary intervention; Polyvascular disease

Atherosclerosis is a systemic inflammatory disorder that often coexists in multiple vascular territories,[1,2] so patients presenting with several atherosclerotic diseases are not rare. Previous studies have reported a clear association between coronary artery disease (CAD) and cerebrovascular disease (CVD).[3–5] In the guideline for dyslipidemia from the European Society of Cardiology, patients with atherosclerotic cardiovascular disease are considered at very high total cardiovascular risk.[6] The occurrence of stroke also has been associated with worse clinical outcomes in patients with stable CAD.[7,8] It has been suggested that patients with acute coronary syndrome (ACS) who have experienced an atherosclerosis-related event such as CAD, CVD or peripheral arterial disease (PAD) are at high risk for developing ischemic events in other vascular territories.[8,9] However, little is known about the relationship between prior stroke and long-term clinical outcomes in patients with ACS. Therefore, the aim of this study was to evaluate the prognostic importance of prior stroke in patients with ACS after treatment with emergency percutaneous coronary intervention (PCI).

Methods

Study Population and Data Collection

Data from a single-center, observational study of consecutive patients who underwent emergency PCI for ACS at

Received January 25, 2021; revised manuscript received March 5, 2021; accepted March 17, 2021; J-STAGE Advance Publication released online April 9, 2021 Time for primary review: 17 days

Department of Cardiovascular Biology and Medicine, Juntendo University Graduate School of Medicine, Tokyo (M.T., Y.O.-N., N.T., T.D., K.M., H.D., T.M.); Department of Cardiovascular Medicine, Juntendo University Shizuoka Hospital, Shizuoka (H.W., M.O., D.T., R.N., K.Y., T.S., S.Y., J.S., S.T., S.S.); and Japan Agency for Medical Research and Development-Core Research for Evolutionary Medical Science and Technology (AMED-CREST), Japan Agency for Medical Research and Development, Tokyo (T.M.), Japan

H.D. is a member of *Circulation Reports*' Editorial Team.

Mailing address: Hideki Wada, MD, PhD, Department of Cardiovascular Medicine, Juntendo University Shizuoka Hospital, 1129 Nagaoka, Izunokuni, Shizuoka 410-2295, Japan. E-mail: hideki06@qj9.so-net.ne.jp

ISSN-2434-0790

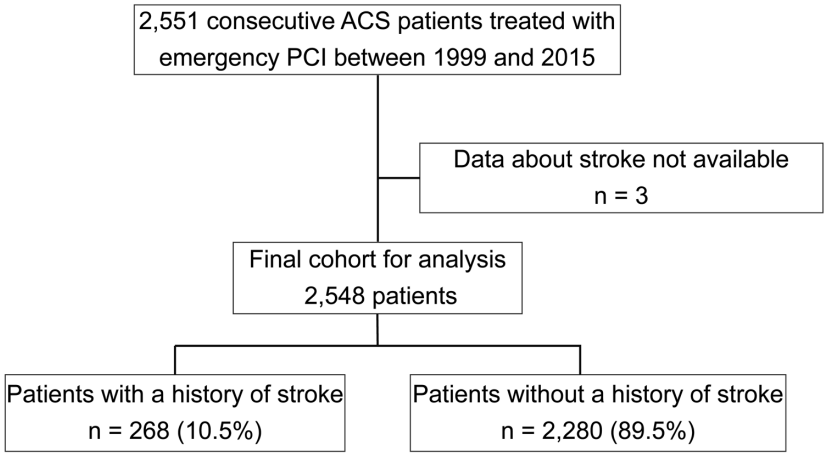

Figure 1. Flow chart of the study. Of the 2,551 consecutive ACS patients treated with the emergency PCI, data of prior stroke were available for 2,548 (99.9%). The patients were divided into 2 groups: with or without a history of stroke on admission. ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.

Juntendo University Shizuoka Hospital between January 1999 and May 2015 were analyzed. ACS was categorized as either unstable angina pectoris (UAP), non-ST-segment elevation myocardial infarction (NSTEMI) or ST-segment elevation myocardial infarction (STEMI). UAP was diagnosed in the presence of ischemic symptoms at rest or having a crescendo of symptoms or new-onset symptoms associated with transient ischemic ST-segment shifts and without release of the enzymes associated with myocardial necrosis. We determined acute myocardial infarction based on symptoms of ischemia and elevated cardiac enzymes, such as troponin. STEMI was diagnosed in the presence of new ST-elevation at the J point in ≥2 contiguous leads. New or presumably new left bundle branch block has been considered as equivalent to STEMI. Patients without ST-segment elevation at presentation were designated NSTEMI. Patients with missing information regarding their history of stroke were excluded from the study.

Demographic data and information about coronary risk factors, medications, revascularization procedure-related factors, and comorbidities were retrospectively collected from medical records in the Juntendo University Shizuoka Hospital database and analyzed. Blood samples were collected before emergency PCI, and blood pressure (BP) was measured on admission. Patients with BP >140/90 mmHg or receiving antihypertensive drugs were regarded as hypertensive. Dyslipidemia was defined as low-density lipoprotein cholesterol (LDL-C) ≥140 mg/dL, high-density lipoprotein cholesterol (HDL-C) ≤40 mg/dL, triglycerides ≥150 mg/dL, or current treatment with statins and/or lipid-lowering agents.[10] Diabetes mellitus was defined as either hemoglobin A1c ≥6.5% or medication with insulin or oral hypoglycemic agents (OHAs). Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, calculated using the Modification of the Diet in Renal Disease equation and modified with a Japanese coefficient using baseline serum creatinine.[11] A current smoker was defined as a person who was smoking at the time of PCI or who had stopped smoking within 1 year before PCI. The left ventricular ejection fraction (LVEF) was assessed by left ventricular angiography or by echocardiography after PCI. Stroke was defined as a neurological function disorder with rapid onset that persisted for at least 24 h or until death, which included only ischemic stroke and excluded hemorrhagic stroke (intracerebral hemorrhage and subarachnoid hemorrhage), transient ischemic attack (defined as focal neurological symptoms lasting <24 h), subdural hemorrhage, epidural hemorrhage, poisoning, and symptoms caused by trauma.

Written informed consent was given by all patients or their families before PCI. This study was performed in accordance with the Declaration of Helsinki and with the approval of the institutional review board.

Primary Endpoints

We evaluated both all-cause death and cardiac death. Cardiac death was defined as death from CAD, cardiogenic shock, or sudden death. Clinical follow-up comprised analyses of office visit charts, responses to questionnaires sent to patients or their families, and telephone contact. Mortality data were collected from the medical records of patients who died or who were treated in Juntendo University Shizuoka Hospital, and details and causes of death were obtained from other hospitals to which patients had been admitted.

Statistical Analysis

Quantitative data are expressed as mean±standard deviation or median and interquartile range (IQR). Categorical variables are presented as frequencies. Continuous variables were compared using unpaired t-tests or Mann-Whitney U-tests. Categorical variables were compared using the chi-squared test or Fisher's exact probability test. Survival curves were estimated using the Kaplan-Meier method, and the log-rank test was used to test for significant differences. Landmark analyses were performed from 0 to 30 days, and from 31 days to the end of follow-up. Effects of prior stroke on clinical outcomes were determined using multivariate Cox proportional hazards regression analysis. Model 1 was unadjusted. Model 2 was adjusted for age and sex. Model 3 was adjusted for variables with established risk factors such as age, sex, hypertension, diabetes mellitus, dyslipidemia, current smoking, family history of CAD, CKD, and hemoglobin. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. $P<0.05$ was considered to indicate statistical significance. All statistical analyses were performed using JMP14.0 (SAS Institute Inc., Cary, NC, USA).

Table 1. Clinical, Angiographic, and Procedural Characteristics of Study Patients

	Overall (n=2,548)	Patients with a history of stroke (n=268)	Patients without a history of stroke (n=2,280)	P value
Baseline characteristic				
Age, years	68.0±11.8	73.3±9.4	67.4±11.9	<0.0001
Male, n (%)	1,867 (73.3)	195 (72.8)	1,672 (73.3)	0.83
Hypertension, n (%)	1,710 (67.1)	204 (76.1)	1,506 (66.0)	0.0007
Diabetes mellitus, n (%)	943 (37.0)	114 (42.5)	829 (36.3)	0.05
Dyslipidemia, n (%)	1,379 (54.1)	136 (50.8)	1,243 (54.5)	0.24
Current smoker, n (%)	1,106 (43.5)	70 (26.2)	1,036 (45.5)	<0.0001
Family history, n (%)	457 (18.3)	36 (13.6)	421 (18.8)	0.04
Multivessel CAD, n (%)	1,116 (43.8)	133 (49.6)	983 (43.1)	0.04
BMI, kg/m^2	23.8±3.7	23.4±3.5	23.9±3.7	0.04
TC, mg/dL	187.7±44.3	177.2±40.1	188.8±44.6	<0.0001
LDL-C, mg/dL	117.2±36.9	107.6±35.0	118.0±36.9	0.002
HDL-C, mg/dL	46.2±13.3	45.1±12.2	46.3±13.4	0.16
TG, mg/dL	76 [48, 120]	68 [45, 110]	77 [49, 120]	0.0002
FBG, mg/dL	138.6±63.0	138.9±67.9	138.6±62.5	0.94
HbA1c, %	6.3±1.4	6.3±1.3	6.3±1.4	0.52
White blood cells, /μL	10,000 [7,900, 13,000]	9,300 [7,300, 11,000]	10,000 [8,000, 13,000]	0.0005
Hemoglobin, g/dL	13.4±3.0	12.7±2.1	13.4±3.1	<0.0001
eGFR, mL/min/1.73m^2	66.0±17.5	60.9±16.0	66.6±17.6	<0.0001
CKD, n (%)	926 (36.4)	130 (48.7)	796 (35.0)	<0.0001
Hemodialysis, n (%)	66 (2.6)	18 (6.7)	48 (2.1)	<0.0001
LVEF, %	59.2±11.5	58.0±11.9	59.3±11.4	0.27
ACS type, n (%)				0.04
UAP	382 (15.0)	52 (19.4)	330 (14.5)	
NSTEMI	202 (7.9)	26 (9.7)	176 (7.7)	
STEMI	1,961 (77.1)	190 (70.9)	1,771 (77.8)	
Prior MI, n (%)	175 (6.9)	22 (8.2)	153 (6.7)	0.37
Prior PCI, n (%)	192 (7.5)	25 (9.3)	167 (7.3)	0.27
Prior CABG, n (%)	49 (1.9)	10 (3.7)	39 (1.7)	0.03
AF, n (%)	196 (7.7)	42 (15.7)	154 (6.8)	<0.0001
Killip class 3–4, n (%)	217 (8.6)	29 (10.8)	188 (8.3)	0.17
Medication at discharge				
ACEI/ARB, n (%)	1,763 (69.2)	177 (66.0)	1,586 (69.6)	0.24
β-blocker, n (%)	902 (35.4)	89 (33.2)	813 (35.7)	0.46
Insulin, n (%)	90 (3.5)	9 (3.4)	81 (3.6)	1.0
OHA, n (%)	419 (16.5)	46 (17.2)	373 (16.4)	0.73
Statin, n (%)	1,701 (66.9)	143 (53.4)	1,558 (68.4)	<0.0001
Aspirin, n (%)	2,224 (87.3)	221 (82.5)	2,003 (87.9)	0.02
P2Y12 inhibitor, n (%)	2,074 (81.4)	210 (78.4)	1,864 (81.8)	0.18
Anticoagulation				0.04
DOAC	14 (0.6)	2 (0.8)	12 (0.5)	
Warfarin	205 (8.1)	32 (11.9)	173 (7.6)	

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CKD, chronic kidney disease; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, Non-ST-elevation MI; OHA, oral hypoglycemic agent; STEMI, ST-elevation MI; TC, total cholesterol; TG, triglycerides; TIMI, Thrombolysis in Myocardial Infarction; UAP, unstable angina pectoris.

Results

Baseline and Procedure Characteristics

Of the 2,551 consecutive ACS patients who were treated with emergency PCI, data about stroke were not available for 3 patients. A total of 268 patients (10.5%) had a history of stroke at the time of admission (**Figure 1**). The clinical and procedural characteristics of these patients are shown in **Table 1**. Patients with a history of stroke were significantly older and had higher prevalences of hypertension, anemia, CKD, hemodialysis, atrial fibrillation, and prior coronary artery bypass grafting (CABG) and relatively

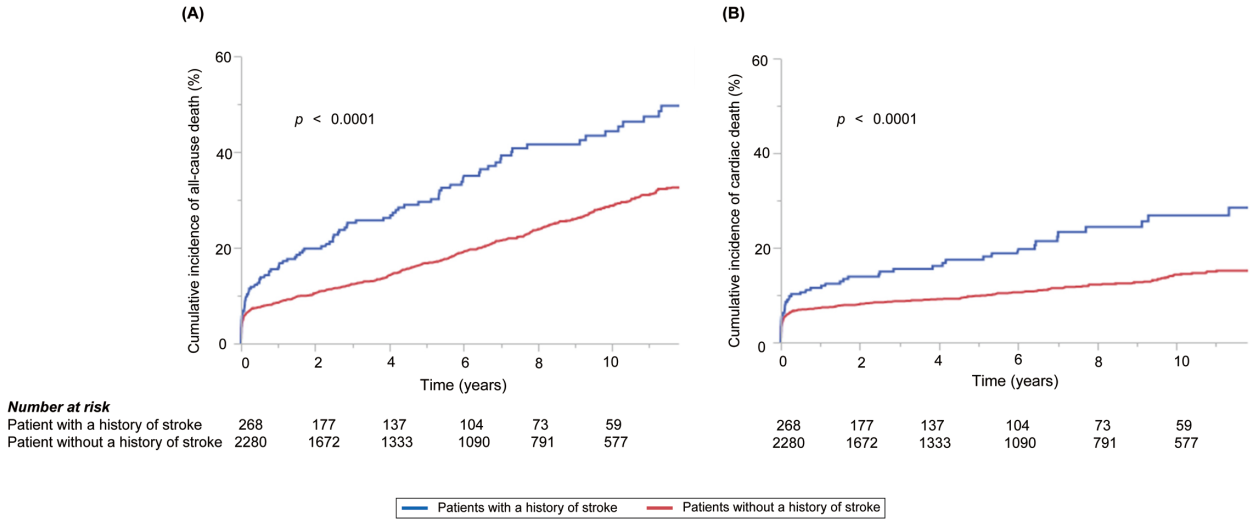

Figure 2. Kaplan-Meier curves for all-cause death (**A**) and cardiac death (**B**). Patients with a history of stroke had higher incidences of all-cause death and cardiac death (both log-rank P<0.0001) compared with those without a history of stroke during follow-up.

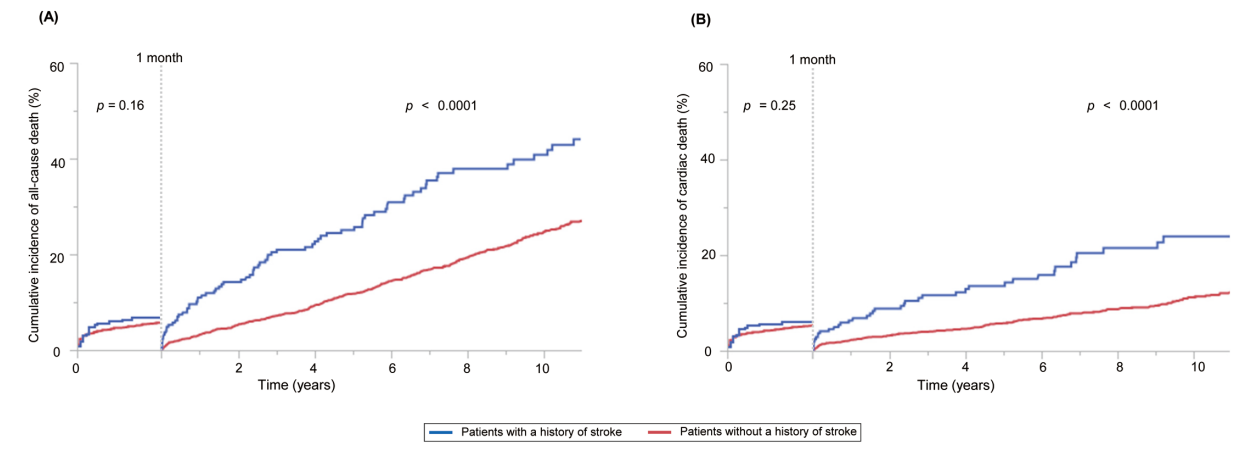

Figure 3. Landmark analysis of Kaplan-Meier curves for all-cause death (**A**) and cardiac death (**B**) with landmark point set at 1 month. Patients with a history of stroke had higher incidences of all-cause death and cardiac death compared with those without a history of stroke during follow-up after 1 month (both log-rank P<0.0001).

lower prevalences of current smoking and lower body mass index (BMI), total cholesterol, LDL-C, triglycerides, and eGFR. Patients with a history of stroke were less likely to be taking statins and aspirin.

Clinical Outcomes

The median follow-up period was 5.3 years (IQR, 1.6–10.0 years). In total, 631 all-cause deaths (frequency, 24.8%) and 309 cardiac deaths (12.4%) were identified during follow-up. **Figure 2** shows the Kaplan-Meier curves for all-cause death and cardiac death. The cumulative incidences of both all-cause death and cardiac death were significantly higher in patients with a history of stroke compared with those without a history of stroke (log-rank test, both P<0.0001). **Figure 3** shows the landmark analysis for all-cause death and cardiac death with landmark point set at 1 month. The patients with a history of stroke had significantly higher incidences of all-cause death and cardiac death after 1 month (log-rank P<0.0001).

Table 2 shows the Cox proportional hazards analysis for all-cause death and cardiac death. In the unadjusted Cox model, prior stroke was significantly associated with all-cause death and cardiac death (both P<0.0001). After adjusting for other covariates, patients with a history of stroke had significantly higher risks of all-cause death (HR, 1.49; 95% CI, 1.20–1.85; P=0.0004) and cardiac death (HR, 1.41; 95% CI, 1.03–1.93; P=0.03) compared with patients without a history of stroke.

Table 2. Cox Proportional Hazards Models for All-Cause Death and Cardiac Death

	All-cause death			Cardiac death		
	HR	95% CI	P value	HR	95% CI	P value
Patients with a history of stroke vs. without a history of stroke						
Model 1	1.92	1.55–2.37	<0.0001	1.85	1.37–2.50	<0.0001
Model 2	1.46	1.18–1.81	0.0004	1.42	1.05–1.92	0.02
Model 3	1.49	1.20–1.85	0.0004	1.41	1.03–1.93	0.03

Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, current smoking, family history of CAD, CKD, and hemoglobin. CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio.

Discussion

The major findings of the present report were as follows: (1) ≈10% of ACS patients had a history of stroke; (2) patients with a history of stroke were older and had more comorbidities such as hypertension or CKD; (3) patients with a history of stroke showed significantly higher incidences of all-cause death and cardiac death than patients without a history of stroke; and (4) even after adjusting for important covariates, prior stroke was significantly associated with worse long-term clinical outcomes in ACS patients undergoing emergency PCI.

Atherosclerosis is a diffuse and systemic disease that is the underlying cause of CAD, CVD, and PAD. These 3 diseases share similar risk factors and frequently coexist.[1,2] In patients with atherosclerosis or with multiple risk factors for atherosclerosis, the presence of clinical involvement of ≥2 arterial beds, so-called 'polyvascular disease (poly VD)', is detected in ≈1 in 6 patients.[12] In the present study, 10.5% of ACS patients had a history of stroke. A similar trend was seen in a previous study reported by Mukherjee et al, in which 15.6% of ACS patients had a history of stroke and/or PAD in the GRACE registry.[13]

Prior stroke was reported as independent factor of in-hospital death with stent thrombosis after drug-eluting stent implantation.[14] Moreover, it has already been reported that the patients with poly VD have a significantly higher risk of in-hospital death,[15] and they showed worse short-term clinical outcomes in the setting of ACS.[16] The present study demonstrated that a history of stroke was significantly associated with all-cause death and cardiac death in ACS patients.

Several mechanisms may contribute to worse clinical outcomes. First, patients with poly VD have worse baseline characteristics.[9,16–18] Meizels et al reported that patients with poly VD were significantly older, more likely to have renal insufficiency, and had a higher prevalence of coronary risk factors.[19] In the present study, the same trends were observed in the backgrounds of patients with a history of stroke, and these patients also had lower hemoglobin levels. Both renal failure[20] and anemia[21] have been reported as independent predictors of worse clinical outcomes after ACS. Therefore, these comorbidities have the potential to also affect the outcomes of patients with a history of stroke.

In addition, in the present study the patients with a history of stroke were less likely to be taking guideline-recommended therapies such as aspirin or statins. One possible reason is that anticoagulant therapies are often needed in patients with a history of stroke due to the higher incidence of atrial fibrillation; therefore, dual antiplatelet therapy (DAPT) might be limited considering the increased risk of bleeding. The present result is consistent with previous studies investigating the prognostic effect of poly VD in patients with ACS.[17,19,22,23] Previous studies reported lower use of guideline-recommended therapies such as DAPT, β-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers and statins in patients with poly VD, despite their higher-risk profiles and even in the absence of contraindications. Another possible explanation for the results of the present study is the effect of functional impairment after stroke. Cognitive impairment is a common consequence of stroke[24] that is associated with lower rates of medication adherence in the cohort of patients hospitalized for ACS.[25] The underuse of guideline-recommended medications and poor medication adherence might explain the relationship between a history of stroke and long-term death.

The previous studies demonstrated that use of guideline-recommended medication is associated with improved outcomes after ACS, even in patients with poly VD.[13,19] In addition, the optimal duration of DAPT recommended in the updated guidelines from the European Society of Cardiology[26] and the Japanese Circulation Society[27] could reduce hemorrhagic events and improve the outcomes in these patients. Based on the results of the present study, patients with a history of stroke have a higher risk of long-term death, and therefore a tailored management plan combining strong risk control and individualized therapy for these patients, considering their poor clinical background, is necessary to improve their outcomes.

Study Limitations

First, as a single-center, observational study of a small patient cohort, unknown confounding factors might have affected the outcomes, regardless of analytical adjustments. Second, data on a history of PAD were not collected. Although previous studies have shown that prior PAD is also an independent predictor of worse clinical outcomes in patients with ACS in addition to prior stroke,[8] the effect of a history of PAD on outcomes after ACS was not assessed in the present study. Third, the history of stroke was only self-reported, not diagnosed by imaging. This may lead to underdiagnosis of stroke, and whether the present findings can be extrapolated to patients with asymptomatic stroke deserves further investigation. Finally, we could not assess the effects of changes in the treatment strategy for ACS and stroke because of the long-term follow-up period. Advances in treatment during the follow-up period might affect the clinical outcomes.

Conclusions

This study demonstrated that a history of stroke was not rare and was associated with a higher risk of long-term all-cause death and cardiac death in ACS patients treated with emergency PCI. Although these patients had worse clinical characteristics, there was low use of evidence-based therapies for them. Efforts to identify and provide individualized therapy might improve their poor clinical outcomes.

Acknowledgments

The authors are grateful to the staff of the Department of Cardiovascular Biology and Medicine at Juntendo University Graduate School of Medicine and the Department of Cardiology at Juntendo University Shizuoka Hospital.

Data Availability

The deidentified participant data will not be shared.

Disclosures

H.D. is a member of *Circulation Reports*' Editorial Team.

IRB Information

This study was approved by the Research Ethics Committee of Juntendo University Shizuoka Hospital (reference no. 406)

References

1. Rothwell PM, Villagra R, Gibson R, Donders RC, Warlow CP. Evidence of a chronic systemic cause of instability of atherosclerotic plaques. *Lancet* 2000; **355:** 19–24.
2. Ross R. Atherosclerosis: An inflammatory disease. *N Engl J Med* 1999; **340:** 115–126.
3. Doonan AL, Karha J, Carrigan TP, Bavry AA, Begelman SM, Ellis SG, et al. Presence of carotid and peripheral arterial disease in patients with left main disease. *Am J Cardiol* 2007; **100:** 1087–1089.
4. Kallikazaros I, Tsioufis C, Sideris S, Stefanadis C, Toutouzas P. Carotid artery disease as a marker for the presence of severe coronary artery disease in patients evaluated for chest pain. *Stroke* 1999; **30:** 1002–1007.
5. Aronow WS, Ahn C. Prevalence of coexistence of coronary-artery disease, peripheral arterial-disease, and atherothrombotic brain infarction in men and women greater-than-or-equal-to-62 years of age. *Am J Cardiol* 1994; **74:** 64–65.
6. Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Atherosclerosis* 2019; **290:** 140–205.
7. Reicher-Reiss H, Jonas M, Tanne D, Mandelzweig L, Goldbourt U, Shotan A, et al. Prognostic significance of cerebrovascular disease in 11,526 chronic coronary artery disease patients: Bezafibrate Infarction Prevention (BIP) Study Group. *Am J Cardiol* 1998; **82:** 1532–1535.
8. Cotter G, Cannon CP, McCabe CH, Michowitz Y, Kaluski E, Charlesworth A, et al. Prior peripheral arterial disease and cerebrovascular disease are independent predictors of adverse outcome in patients with acute coronary syndromes: Are we doing enough? Results from the Orbofiban in Patients with Unstable Coronary Syndromes-Thrombolysis In Myocardial Infarction (OPUS-TIMI) 16 study. *Am Heart J* 2003; **145:** 622–627.
9. Consuegra-Sanchez L, Melgarejo-Moreno A, Galcera-Tomas J, Alonso-Fernandez N, Diaz-Pastor A, Escudero-Garcia G, et al. Impact of previous vascular burden on in-hospital and long-term mortality in patients with ST-segment elevation myocardial infarction. *Rev Esp Cardiol (Engl Ed)* 2014; **67:** 471–478.
10. Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi S, et al. Diagnostic criteria for dyslipidemia. *J Atheroscler Thromb* 2013; **20:** 655–660.
11. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; **53:** 982–992.
12. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006; **295:** 180–189.
13. Mukherjee D, Eagle KA, Kline-Rogers E, Feldman LJ, Juliard JM, Agnelli G, et al. Impact of prior peripheral arterial disease and stroke on outcomes of acute coronary syndromes and effect of evidence-based therapies (from the Global Registry of Acute Coronary Events). *Am J Cardiol* 2007; **100:** 1–6.
14. Mitsutake Y, Konishi A, Handa N, Ho M, Shirato H, Ito T, et al. Independent factors for in-hospital death following drug-eluting stent thrombosis from the Japanese Adverse Event Report System. *Circ J* 2020; **84:** 1568–1574.
15. Bhatt DL, Peterson ED, Harrington RA, Ou FS, Cannon CP, Gibson CM, et al. Prior polyvascular disease: Risk factor for adverse ischaemic outcomes in acute coronary syndromes. *Eur Heart J* 2009; **30:** 1195–1202.
16. Cordeiro F, Mateus PS, Ferreira A, Leao S, Moz M, Moreira JI, et al. Short-term prognostic effect of prior cerebrovascular and peripheral artery disease in patients with acute coronary syndrome: Can we do better? *Eur Heart J Acute Cardiovasc Care* 2018; **7:** 652–660.
17. Lee TC, Goodman SG, Yan RT, Grondin FR, Welsh RC, Rose B, et al. Disparities in management patterns and outcomes of patients with non-ST-elevation acute coronary syndrome with and without a history of cerebrovascular disease. *Am J Cardiol* 2010; **105:** 1083–1089.
18. Ducrocq G, Amarenco P, Labreuche J, Alberts MJ, Mas JL, Ohman EM, et al. A history of stroke/transient ischemic attack indicates high risks of cardiovascular event and hemorrhagic stroke in patients with coronary artery disease. *Circulation* 2013; **127:** 730–738.
19. Meizels A, Zeitoun DM, Bataille V, Cambou JP, Collet JP, Cottin Y, et al. Impact of polyvascular disease on baseline characteristics, management and mortality in acute myocardial infarction: The Alliance project. *Arch Cardiovasc Dis* 2010; **103:** 207–214.
20. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004; **351:** 1285–1295.
21. Wang X, Qiu M, Qi J, Li J, Wang H, Li Y, et al. Impact of anemia on long-term ischemic events and bleeding events in patients undergoing percutaneous coronary intervention: A system review and meta-analysis. *J Thorac Dis* 2015; **7:** 2041–2052.
22. Froehlich JB, Mukherjee D, Avezum A, Budaj A, Kline-Rogers EM, Lopez-Sendon J, et al. Association of peripheral artery disease with treatment and outcomes in acute coronary syndromes: The Global Registry of Acute Coronary Events (GRACE). *Am Heart J* 2006; **151:** 1123–1128.
23. Subherwal S, Bhatt DL, Li S, Wang TY, Thomas L, Alexander KP, et al. Polyvascular disease and long-term cardiovascular outcomes in older patients with non-ST-segment-elevation myocardial infarction. *Circ Cardiovasc Qual Outcomes* 2012; **5:** 541–549.
24. Lesniak M, Bak T, Czepiel W, Seniow J, Czlonkowska A. Frequency and prognostic value of cognitive disorders in stroke patients. *Dement Geriatr Cogn Disord* 2008; **26:** 356–363.
25. Marzec LN, Carey EP, Lambert-Kerzner AC, Del Giacco EJ, Melnyk SD, Bryson CL, et al. Cognitive dysfunction and poor health literacy are common in veterans presenting with acute coronary syndrome: Insights from the MEDICATION study. *Patient Prefer Adherence* 2015; **9:** 745–751.
26. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018; **39:** 213–260.
27. Nakamura M, Kimura K, Kimura T, Ishihara M, Otsuka F, Kozuma K, et al. JCS 2020 Guideline focused update on antithrombotic therapy in patients with coronary artery disease. *Circ J* 2020; **84:** 831–865.