Circulation Reports
Circ Rep 2023; 5: 198–209
doi:10.1253/circrep.CR-23-0029

ORIGINAL ARTICLE
Ischemic Heart Disease

Incidence of Mid-Term Prognostic Events in Patients With Acute Coronary Syndrome During the Late 2010s in 2 Tertiary Hospitals in a Rural Area of Japan

— A Temporal Comparison —

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Background: Data on the incidence of mid-term prognostic events in patients who developed acute coronary syndrome (ACS) in the late 2010s are scarce.

Methods and Results: We retrospectively included and collected data for 889 patients with ACS (ST-elevation myocardial infarction [STEMI]/non-ST-elevation ACS [NSTE-ACS]) discharged alive from 2 tertiary hospitals in Izumo City, in rural Japan, between August 2009 and July 2018. Patients were divided into 3 time groups (T1: August 2009–July 2012; T2: August 2012–July 2015; T3: August 2015–July 2018). The cumulative incidence of major adverse cardiovascular events (MACE; comprising all-cause death, recurrent ACS, and stroke), major bleeding, and heart failure hospitalization within 2 years of discharge was compared among the 3 groups. The incidence of freedom from MACE was significantly higher in the T3 group than in the T1 and T2 groups (93 [95% confidence interval {CI} 90–96%] vs. 86% [95% CI 83–90] and 89% [95% CI 90–96], respectively; P=0.03). There was a tendency for a higher incidence of STEMI among patients in T3 (P=0.057). The incidence of NSTE-ACS was comparable among the 3 groups (P=0.31), as was the incidence of major bleeding and hospitalization for heart failure.

Conclusions: The incidence of mid-term MACE in patients who developed ACS during the late 2010s (2015–2018) was lower than that in prior periods (2009–2015).

Key Words: Acute coronary syndrome; Major adverse cardiovascular events; ST-elevation myocardial infarction

Cardiovascular diseases are a universal healthcare issue because they are the leading cause of death worldwide.[1] Acute myocardial infarction (AMI) accounts for the major burden of all cardiovascular diseases. With the development of guidelines, evidence-based therapeutic strategies for AMI, such as early primary percutaneous coronary intervention (PCI) and optimal medical therapy, have been implemented mainly in Western countries since the 2000s.[2,3] Because of this, significant improvements in the prognosis of AMI during the acute and chronic periods have been observed in some countries.[4–6] However, most reports compared data from the 1990s, when guideline-based management had not been developed, with date from the 2000s, when management prevailed. Hence, the prognostic information for AMI in the 2010s, when an evidence-based therapeutic strategy was established, remains to be elucidated. In particular, data from the late 2010s are limited. One may infer that the prognosis of AMI during the chronic period in recent clinical settings could have improved further due to the widespread use of conventional evidence-based therapeutic agents, new PCI devices (e.g., new-generation drug-eluting

Received March 14, 2023; revised manuscript received March 22, 2023; accepted March 24, 2023; J-STAGE Advance Publication released online April 20, 2023 Time for primary review: 4 days

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ISSN-2434-0790

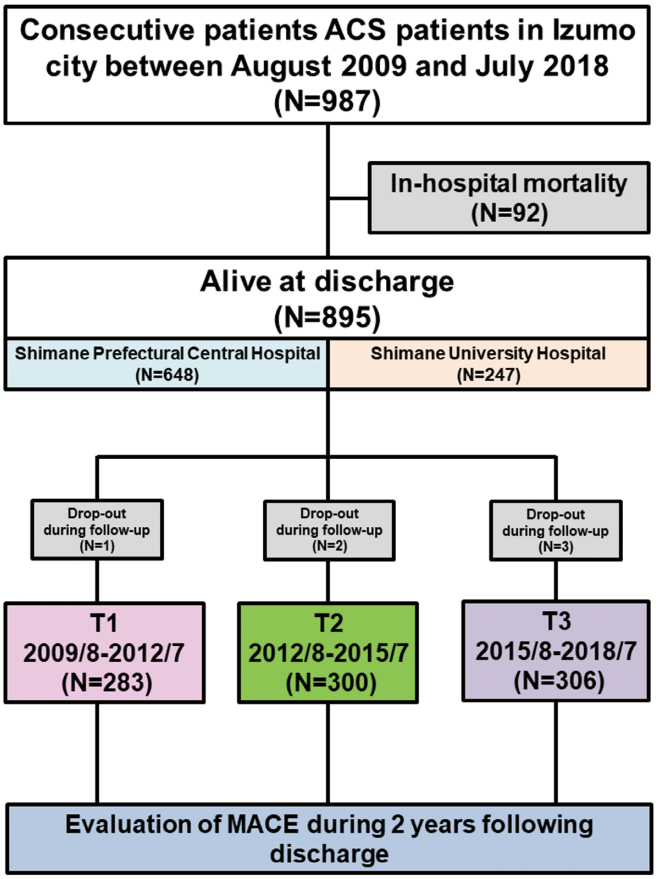

Figure 1. Flow diagram of the study. Patients were divided into 3 time groups: T1 (August 2009–July 2012), T2 (August 2012–July 2015), and T3 (August 2015–July 2018). ACS, acute coronary syndrome; MACE, major adverse cardiovascular event.

stents [DES]), and new therapeutic agents (e.g., new-generation thienopyridine, non-statin lipid-lowering agents, direct oral anticoagulants, and sodium-glucose cotransporter 2 inhibitors). To address this issue, we compared the mid-term prognosis of acute coronary syndrome (ACS) between the late 2010s and prior periods by analyzing the incidence of mid-term clinical events in patients who developed ACS between 2009 and 2018 in a rural area of Japan.

Methods

Study Design

This retrospective 2-institutional historical cohort study was conducted using a database from our previous studies.[7,8] The requirement for informed consent was waived because this study used an opt-out system. The study was performed in accordance with the Declaration of Helsinki and the ethical standards of The Institutional Review Boards of ShimanePrefectural Central Hospital (Churin R20-64) and Shimane University Hospital (20220206-1) approved this study. The institutional review boards of Shimane Prefectural Central Hospital and Shimane University Hospital approved the study. Both institutions are tertiary hospitals in Izumo City, Shimane Prefecture, located in a rural area in southwest Japan. Izumo city has 174,530 inhabitants, and the population has been stable over the past 10 years.[7] PCI and cardiac care units are not available in the city other than at Shimane Prefectural Central Hospital and Shimane University Hospital.[7]

The present study included patients who fulfilled the following criteria: (1) those who were admitted based on a diagnosis of ACS at either of the 2 institutions between August 2009 and July 2018; (2) those who were habitants of Izumo City; and (3) those who were discharged alive. Patients were divided into 3 groups according to admission date: T1 (August 2009–July 2012), T2 (August 2012–July 2015), and T3 (August 2015–July 2018). The cumulative incidence of major adverse cardiovascular events (MACE) within 2 years of discharge was compared among the 3 temporal groups. Patients censored for reasons other than death were excluded. Clinical data were collected for review from the electronic medical records of each institution, as described previously.[7,8]

Study Endpoints

The primary endpoint of the study was the cumulative incidence of MACE within 2 years of discharge. MACE included all-cause death, recurrence of ACS, and stroke. Secondary endpoints were the cumulative incidence of major bleeding and hospitalization for heart failure within 2 years of discharge.

Diagnostic Criteria

As described previously,[7] ACS was diagnosed based on ischemic symptoms with electrocardiographic changes and/or abnormal myocardial wall motion determined using echocardiography. ACS comprised ST-elevation myocardial infarction (STEMI) and non-ST-elevation ACS (NSTE-ACS).

NSTE-ACS was subdivided into non-STEMI (NSTEMI) and unstable angina pectoris. STEMI/NSTEMI was diagnosed when cardiac troponin or high-sensitivity cardiac troponin were above the 99th percentile.[9] Planned coronary revascularization for the target lesion or revascularization for asymptomatic patients was not considered for clinical events. Stroke was diagnosed as a neurological symptom, with plausible abnormal findings obtained using imaging modalities. Major bleeding events were defined as bleeding with a severity of ≥3 according to the Bleeding Academic Research Consortium criteria.[10]

Patient Follow-up

Patients who underwent implantation of bare-metal stents (BMSs) were treated with dual antiplatelet therapy (DAPT) with concomitant use of acetylsalicylic acid (ASA) and a $P2Y_{12}$ receptor inhibitor (clopidogrel/prasugrel) for at least 1 month. Patients who underwent implantation of DES were maintained on DAPT for at least 1 year. The duration of DAPT was modified according at the discretion of the attending cardiologist. Following DAPT completion, lifelong monotherapy with ASA or $P2Y_{12}$ inhibitors was continued.

Changes in Practice for ACS During the Study Period

Although new-generation DES were available during the entire study period, the implantation of DES for patients with ACS was not covered by Japanese National Health Insurance before June 2011. A high-sensitivity cardiac troponin assay was available from April 2012 at Shimane University and from November 2014 at Shimane Prefectural Central Hospital. Prasugrel has been commercially available since May 2014. Although ticagrelor and proprotein convertase subtilisin/kexin type 9 inhibitors were commercially available from around 2016 and 2017, neither of the agents was regularly available at the 2 institutions during the study period.

Statistical Analysis

Normally distributed variables are presented as the mean±SD. Non-normally distributed variables are presented as the median and interquartile range (IQR). The significance of differences in continuous variables between the groups was determined using analysis of variance (ANOVA). Categorical variables are expressed as frequencies and percentages, and were compared using the Chi-squared test. The significance of differences in the cumulative incidence of each endpoint were compared using log-rank tests. Temporal differences were subsequently analyzed using a post hoc pairwise comparison of the log-rank test. All analyses were performed using SPSS version 19 (IBM Corp., Armonk, NY, USA), and 2-sided $P<0.05$ was considered statistically significant. To account for multiple comparisons using Bonferroni correction, the statistical

Table 1. Patient Demographics in the Total ACS Population and Over Time

	Total (n=889)	T1 (n=283)	T2 (n=300)	T3 (n=306)	P value
Age (years)	70±12	69±12	71±12	70±12	0.19
Male sex	655 (74)	207 (73)	215 (72)	233 (76)	0.44
BMI (kg/m²)	24±4	23±3	24±4	24±4	0.1
Time from symptom onset to arrival (h)	3 [1–10]	3 [1.1–12]	2.5 [1–7.2]	3 [1–11]	0.15
CPA at presentation	39 (4)	14 (5)	13 (4)	12 (4)	0.83
PCI	795 (89)	254 (90)	272 (91)	269 (88)	0.53
CABG	44 (5)	15 (5)	10 (3)	19 (6)	0.25
Conservative therapy	56 (6)	14 (5)	20 (7)	22 (7)	0.51
Use of BMS*	226 (25)	189 (67)	33 (11)	4 (1)	<0.0001
Use of first-generation DES*	5 (1)	5 (2)	0	0	0.004
Use of new-generation DES*	514 (58)	57 (20)	219 (73)	238 (78)	<0.0001
Peak CK (IU/L)	1,066 [229–2,467]	1,173 [226–2,525]	996 [207–2,504]	1,074 [302–2,277]	0.27
Killip Class III/IV	106 (12)	42 (15)	30 (10)	34 (11)	0.17
Hospital stay (days)	13 [8–19]	14 [10–20]	13 [7–19]	13 [8–19]	0.68
Use of hs-cTn assay*	448 (50)	4 (1)	138 (46)	306 (100)	<0.0001
STEMI	558 (63)	176 (62)	193 (64)	189 (62)	0.78
NSTE-ACS	331 (37)	107 (38)	107 (36)	117 (38)	0.78
NSTEMI*	221 (25)	65 (23)	64 (21)	92 (30)	0.03
UAP*	110 (12)	42 (15)	43 (14)	25 (8)	0.02
NSTEMI without CK elevation	91 (10)	22 (8)	28 (9)	41 (13)	0.06
NSTEMI with CK elevation	130 (15)	43 (15)	36 (12)	51 (17)	0.25
Involving LAD lesion	468 (53)	147 (52)	160 (53)	161 (53)	0.94
History of PCI	109 (12)	28 (10)	44 (15)	37 (12)	0.21
History of CABG	10 (1)	4 (1)	6 (2)	0	0.06
Current smoker	270 (30)	88 (31)	92 (31)	90 (29)	0.89
Past smoker*	262 (29)	64 (23)	96 (32)	102 (33)	0.008

(**Table 1** continued the next page.)

	Total (n=889)	T1 (n=283)	T2 (n=300)	T3 (n=306)	P value
Status at discharge					
Hypertension*	617 (69)	174 (61)	216 (72)	227 (74)	0.001
Dyslipidemia	528 (59)	154 (54)	188 (63)	186 (61)	0.11
Diabetes	334 (38)	94 (33)	125 (42)	115 (38)	0.11
Atrial fibrillation	105 (12)	40 (14)	26 (9)	39 (13)	0.1
History of bleeding	76 (9)	22 (8)	30 (10)	24 (8)	0.54
History of stroke	92 (10)	21 (7)	36 (12)	35 (11)	0.14
Active cancer*	37 (4)	3 (1)	20 (7)	14 (5)	0.002
Creatinine (mg/dL)	0.81 [0.66–1.01]	0.79 [0.66–0.98]	0.85 [0.68–1.08]	0.79 [0.66–0.96]	0.81
LDL-C (mg/dL)	98±34	99±37	97±31	98±34	0.84
HDL-C (mg/dL)*	46±14	45±14	45±14	48±13	0.01
CRP (mg/dL)	0.2 [0.07–0.83]	0.2 [0.07–0.9]	0.2 [0.06–0.74]	0.2 [0.08–0.92]	0.86
LVEF (%)	51±11	50±11	51±11	51±10	0.24
ASA*	841 (95)	275 (97)	287 (96)	279 (91)	0.003
Cilostazol*	12 (1)	10 (4)	1 (0.3)	1 (0.3)	<0.0001
Clopidogrel*	630 (71)	246 (87)	242 (81)	142 (46)	<0.0001
Prasugrel*	142 (16)	0	30 (10)	112 (37)	<0.0001
ACEI/ARB	645 (72)	207 (73)	218 (73)	220 (72)	0.94
β-blocker	627 (70)	205 (72)	198 (66)	224 (73)	0.1
CCB	171 (19)	50 (18)	62 (21)	59 (19)	0.66
Statin	798 (90)	259 (92)	266 (89)	273 (89)	0.49
EPA*	100 (11)	37 (13)	49 (16)	14 (5)	0.0001
Ezetimibe*	28 (3)	3 (1)	9 (3)	16 (5)	0.01
Diuretics	258 (29)	92 (33)	82 (27)	84 (27)	0.29
OHA/insulin*	217 (24)	51 (18)	90 (30)	76 (25)	0.003
SGLT2 inhibitor*	8 (1)	0	0	8 (3)	0.0004
Warfarin*	85 (10)	46 (16)	23 (8)	16 (5)	<0.0001
DOACs*	35 (4)	2 (1)	6 (2)	27 (9)	<0.0001

Unless indicated otherwise, data are presented as the mean±SD, as the median [interquartile range], or as n (%). *Statistical significance (P<0.05). Patients were divided into 3 time groups: T1 (August 2009–July 2012), T2 (August 2012–July 2015), and T3 (August 2015–July 2018). ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; ASA, acetylsalicylic acid; BMI, body mass index; BMS, bare-metal stent; CABG, coronary artery bypass graft; CCB, calcium channel blockers; CK, creatine kinase; CPA, cardiopulmonary arrest; CRP, C-reactive protein; DES, drug-eluting stent; DOACs, direct oral anticoagulants; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; hs-cTn; high-sensitivity cardiac troponin; LAD, left anterior descending artery; LDL-C, low density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; OHA, oral hypoglycemic agent; PCI, percutaneous coronary intervention; SGLT2; sodium-glucose cotransporter-2; STEMI, ST-segment elevation myocardial infarction; UAP, unstable angina pectoris.

significance of post hoc pairwise comparisons was established at a threshold of P<0.017.

Results

Patient Population

The flow diagram for the study is shown in **Figure 1**. During the entire study period, 987 patients living in Izumo City were diagnosed with ACS at the 2 institutions. Of these patients, 92 were excluded because of in-hospital mortality, with no significant differences among the 3 groups (P=0.32). Ultimately, 283, 300, and 306 patients were categorized into the T1, T2, and T3 groups, respectively.

Patient Demographics for the Total ACS Population

The patient demographics of the total population are presented in **Table 1**. Demographic characteristics (e.g., age, sex, body mass index, Killip class, time from symptom onset to arrival, and the proportion of cardiopulmonary arrests at presentation) were comparable among the 3 temporal groups. Parameters associated with therapeutic strategy, the proportion of PCI, coronary artery bypass grafting (CABG), and conservative therapy were also comparable among the 3 groups. The use of new-generation DES increased significantly over time, along with a decrease in the use of BMS. The proportion of patients taking prasugrel increased significantly over time, whereas the proportion of patients taking ASA and cilostazol decreased significantly. The use of conventional guideline-recommended agents, such as angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor blockers (ARB), β-blockers, and statins, was consistently high among the groups. In response to the decrease in warfarin use, the use of direct oral anticoagulants increased significantly over time.

Demographics of Patients With STEMI or NSTE-ACS

The demographics of patients according to the presence of STEMI or NSTE-ACS are summarized in **Table 2**. The proportion of STEMI among all patients with ACS was consistently high in the 3 temporal groups. Among patients with NSTE-ACS, the proportion of NSTEMI without elevated creatinine kinase increased significantly over time, with a decrease in the proportion of patients with unstable angina pectoris. The proportion of patients with STEMI

Table 2. Patient Demographics in Patients With STEMI and NSTE-ACS in Total and Over Time

Patients with STEMI	Total (n=558)	T1 (n=176)	T2 (n=193)	T3 (n=189)	P value
Age (years)	69±12	69±12	71±12	69±12	0.15
Male sex	412 (74)	127 (72)	141 (73)	144 (76)	0.63
BMI (kg/m^2)	23±4	23±3	23±3	24±4	0.08
Time from symptom onset to arrival (h)	2.5 [1–7]	2.5 [1–6]	2 [1–5]	3 [1–8.4]	0.26
CPA at presentation	35 (6)	11 (6)	13 (7)	11 (6)	0.84
PCI	528 (95)	164 (93)	184 (95)	180 (95)	0.58
CABG	8 (1)	4 (2)	2 (1)	2 (1)	0.52
Conservative therapy	24 (4)	8 (5)	8 (4)	8 (4)	0.98
Use of BMS*	157 (28)	136 (77)	20 (10)	1 (1)	<0.0001
Use of first-generation DES	1 (0.2)	1 (1)	0	0	0.33
Use of new-generation DES*	340 (61)	25 (14)	151 (78)	164 (87)	<0.0001
Peak CK (IU/L)	1,760 [855–3,179]	1,962 [996–3,253]	1,704 [855–3,456]	1,695 [730–2,889]	0.1
Killip Class III/IV	71 (13)	26 (15)	23 (12)	22 (12)	0.45
Hospital stay (days)	14 [11–20]	15 [13–20]	14 [10–20]	14 [10–20]	0.68
Use of hs-cTn assay*	275 (49)	2 (1)	84 (44)	189 (100)	<0.0001
Involving LAD lesion	284 (51)	85 (48)	105 (54)	94 (50)	0.44
History of PCI	47 (8)	14 (8)	19 (10)	14 (7)	0.67
History of CABG	3 (1)	2 (1)	1 (1)	0	0.33
Current smoker	188 (34)	64 (36)	64 (33)	60 (32)	0.61
Past smoker*	154 (28)	33 (19)	61 (32)	60 (32)	0.007
Status at discharge					
Hypertension*	378 (68)	102 (58)	143 (74)	133 (70)	0.002
Dyslipidemia	336 (60)	94 (53)	119 (62)	123 (65)	0.07
Diabetes	202 (36)	61 (35)	75 (39)	66 (35)	0.58
Atrial fibrillation*	61 (11)	28 (16)	15 (8)	18 (10)	0.03
History of bleeding	43 (8)	11 (6)	19 (10)	13 (7)	0.28
History of stroke	49 (9)	13 (7)	20 (10)	16 (8)	0.59
Active cancer*	19 (3)	1 (1)	10 (5)	8 (4)	0.04
Creatinine (mg/dL)	0.8 [0.65–0.98]	0.78 [0.65–0.96]	0.83 [0.65–1.07]	0.79 [0.65–0.96]	0.92
LDL-C (mg/dL)	99±34	100±37	98±32	98±34	0.79
HDL-C (mg/dL)	46±14	45±14	45±14	48±13	0.06
CRP (mg/dL)	0.17 [0.07–0.76]	0.16 [0.07–0.81]	0.17 [0.06–0.7]	0.2 [0.07–0.81]	0.84
LVEF (%)	49±10	48±10	50±11	50±9	0.09
ASA*	533 (96)	174 (99)	185 (96)	174 (92)	0.004
Cilostazol*	7 (1)	6 (3)	1 (0.5)	0	0.007
Clopidogrel*	403 (72)	158 (90)	160 (83)	85 (45)	<0.0001
Prasugrel*	100 (18)	0	18 (9)	82 (43)	<0.0001
ACEI/ARB	455 (82)	144 (82)	163 (84)	148 (78)	0.29
β-blocker*	425 (76)	142 (81)	135 (70)	148 (78)	0.03
CCB	75 (13)	16 (9)	27 (14)	32 (17)	0.09
Statin*	515 (92)	167 (95)	171 (89)	177 (94)	0.03
EPA*	59 (11)	20 (11)	32 (17)	7 (4)	0.0002
Ezetimibe*	19 (3)	2 (1)	5 (3)	12 (6)	0.02
Diuretics	181 (32)	67 (38)	56 (29)	58 (31)	0.16
OHA/insulin*	134 (24)	33 (19)	59 (31)	42 (22)	0.02
SGLT2 inhibitor*	6 (1)	0	0	6 (3)	0.002
Warfarin*	48 (9)	27 (15)	13 (7)	8 (4)	0.0004
DOACs*	21 (4)	2 (1)	5 (3)	14 (7)	0.004

(**Table 2** continued the next page.)

Patients with NSTE-ACS	Total (n=331)	T1 (n=107)	T2 (n=107)	T3 (n=117)	P value
Age (years)	71±12	70±12	71±12	72±11	0.53
Male sex	243 (73)	80 (75)	74 (69)	89 (76)	0.46
BMI (kg/m^2)	24±4	23±3	24±4	24±4	0.74
Time from symptom onset to arrival (h)	3 [1.5–12]	4 [2–24]	3 [1.5–11]	3 [1.4–11]	0.11
CPA at presentation	4 (1)	3 (3)	0	1 (1)	0.15
PCI	267 (81)	90 (84)	88 (82)	89 (76)	0.27
CABG	36 (11)	11 (10)	8 (7)	17 (15)	0.23
Conservative therapy	32 (10)	6 (6)	12 (11)	14 (12)	0.22
Use of BMS*	69 (21)	53 (50)	13 (12)	3 (3)	<0.0001
Use of first-generation DES*	4 (1)	4 (4)	0	0	0.01
Use of new-generation DES*	174 (53)	32 (30)	68 (64)	74 (63)	<0.0001
Peak CK (IU/L)	192 [92–630]	162 [87–647]	193 [93–391]	227 [99–863]	0.64
Killip Class III/IV	35 (11)	16 (15)	7 (7)	12 (10)	0.13
Hospital stay (days)	10 [4–18]	12 [4–19]	7 [3–18]	10 [4–17]	0.73
Use of hs-cTn assay*	173 (52)	2 (2)	54 (50)	117 (100)	<0.0001
NSTEMI*	221 (67)	65 (61)	64 (60)	92 (79)	0.003
UAP*	110 (33)	42 (39)	43 (40)	25 (21)	0.003
NSTEMI without CK elevation*	91 (27)	22 (21)	28 (26)	41 (35)	0.049
NSTEMI with CK elevation	130 (39)	43 (40)	36 (34)	51 (44)	0.31
Involving LAD lesion	184 (56)	62 (58)	55 (51)	67 (57)	0.56
History of PCI	62 (19)	14 (13)	25 (23)	23 (20)	0.14
History of CABG	7 (2)	2 (2)	5 (5)	0	0.051
Current smoker	82 (25)	24 (22)	28 (26)	30 (26)	0.78
Past smoker	108 (33)	31 (29)	35 (33)	42 (36)	0.54
Status at discharge					
Hypertension*	239 (72)	72 (67)	73 (68)	94 (80)	0.049
Dyslipidemia	192 (58)	60 (56)	69 (64)	63 (54)	0.24
Diabetes	132 (40)	33 (31)	50 (47)	49 (42)	0.051
Atrial fibrillation	44 (13)	12 (11)	11 (10)	21 (18)	0.17
History of bleeding	33 (10)	11 (10)	11 (10)	11 (9)	0.96
History of stroke	43 (13)	8 (7)	16 (15)	19 (16)	0.11
Active cancer	18 (5)	2 (2)	10 (9)	6 (5)	0.053
Creatinine (mg/dL)	0.83 [0.68–1.02]	0.84 [0.68–1]	0.72 [0.48–1.1]	0.77 [0.66–0.95]	0.8
LDL-C (mg/dL)	98±33	98±36	97±29	98±34	0.96
HDL-C (mg/dL)	46±14	46±13	45±13	48±14	0.19
CRP (mg/dL)	0.2 [0.08–0.95]	0.23 [0.07–0.91]	0.18 [0.07–0.78]	0.24 [0.08–1.09]	0.73
LVEF (%)	54±12	53±13	55±11	53±12	0.62
ASA	308 (93)	101 (94)	102 (95)	105 (90)	0.21
Cilostazol*	5 (1)	4 (4)	0	1 (1)	0.06
Clopidogrel*	227 (69)	88 (82)	82 (77)	57 (49)	<0.0001
Prasugrel*	42 (13)	0	12 (11)	30 (26)	<0.0001
ACEI/ARB	190 (57)	63 (59)	55 (51)	72 (62)	0.28
β-blocker	202 (61)	63 (59)	63 (59)	76 (65)	0.55
CCB	96 (29)	34 (32)	35 (33)	27 (23)	0.21
Statin	283 (85)	92 (86)	95 (89)	96 (82)	0.35
EPA*	41 (12)	17 (16)	17 (16)	7 (6)	0.03
Ezetimibe*	9 (3)	1 (1)	4 (4)	4 (3)	0.38
Diuretics	77 (23)	25 (23)	26 (24)	26 (22)	0.93
OHA/insulin*	83 (25)	18 (17)	31 (30)	34 (29)	0.04
SGLT2 inhibitor	2 (1)	0	0	2 (2)	0.16
Warfarin*	37 (11)	19 (18)	10 (9)	8 (7)	0.02
DOACs*	14 (4)	0	1 (1)	13 (11)	<0.0001

Unless indicated otherwise, data are presented as the mean±SD, as the median [interquartile range], or as n (%). *Statistical significance (P<0.05). Patients were divided into 3 time groups: T1 (August 2009–July 2012), T2 (August 2012–July 2015), and T3 (August 2015–July 2018). Abbreviations as in Table 1.

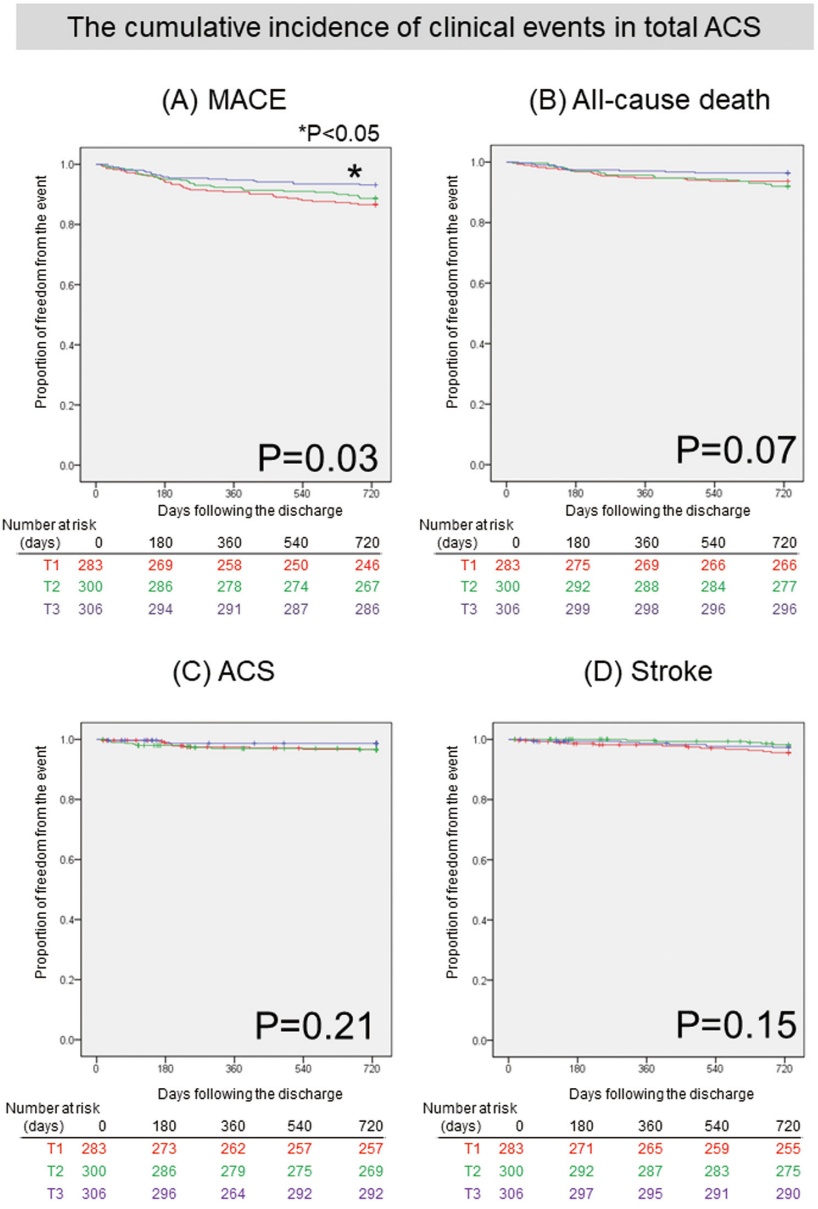

Figure 2. Cumulative incidence of clinical events in the total acute coronary syndrome (ACS) population in this study over time. (**A**) Freedom from major adverse cardiovascular events (MACE), (**B**) freedom from all-cause death, (**C**) freedom from recurrent of ACS, and (**D**) freedom from stroke. Patients were divided into 3 time groups: T1 (August 2009–July 2012; red), T2 (August 2012–July 2015; green), and T3 (August 2015–July 2018; purple). *Difference between groups (P<0.05).

who underwent PCI was consistently high. In patients with NSTE-ACS, although the proportion of patients undergoing PCI decreased slightly over time, the proportion undergoing CABG increased. The proportion of patients with atrial fibrillation was significantly lower in those with STEMI. In contrast, the proportion of patients with atrial fibrillation was significantly higher among those with NSTE-ACS. The proportion of patients with active cancer increased significantly in the STEMI and NSTE-ACS groups.

Incidence of MACE in the Total ACS Population Over Time

The incidence of MACE and related clinical events in the total ACS population, as well as in each of the T1, T2, and T3 groups, are presented in **Figure 2** and **Table 3**. Freedom from MACE was higher in the T3 than T1 and T2 groups (T1 vs. T2 vs. T3 93% [95% confidence interval {CI} 90–96%], vs. 86% [95% CI 83–90%] and 89% [95% CI 90–96%], respectively; P=0.03). In particular, the difference in the incidence of MACE was significantly greater between the T1 and T3 groups (P=0.008). In terms of the clinical events that comprised MACE, freedom from all-cause death was higher in the T3 than T1 and T2 groups (96% [95% CI 94–98%] vs. 93% [95% CI 91–96%] and 92% [95% CI 89–95%], respectively; P=0.07). In particular, the difference in all-cause death was greater between the T3 and T2 groups (P=0.02). Freedom from ACS recurrence was higher in the T2 than T3 group, but the difference did not reach statistical significance (P=0.09). There was a significant difference in the freedom from stroke between the T1 and T2 groups (P=0.06).

Incidence of MACE in Patients With STEMI or NSTE-ACS

The incidence of MACE and related clinical events in

Table 3. Cumulative Incidence of Freedom From Major Clinical Events in the Total ACS Population, in Patients With STEMI, and in Patients With NSTE-ACS Over Time

	Cumulative incidence (%) with 95% CI				P value (post hoc pairwise comparisons)		
	T1	T2	T3	P value	T1 vs. T2	T1 vs. T3	T2 vs. T3
Total ACS population							
MACE*	86 (83–90)	89 (85–92)	93 (90–96)	0.03	0.43	0.008	0.058
All-cause death	93 (91–96)	92 (89–95)	96 (94–98)	0.07	0.46	0.12	0.02
ACS	97 (94–99)	97 (94–99)	99 (97–100)	0.21	0.91	0.12	0.09
Stroke	96 (93–98)	98 (97–100)	97 (95–99)	0.15	0.06	0.25	0.44
Patients with STEMI							
MACE	87 (83–92)	91 (87–95)	95 (91–98)	0.057	0.26	0.016	0.18
All-cause death	94 (91–98)	93 (90–97)	98 (96–100)	0.09	0.7	0.07	0.03
ACS	98 (96–100)	97 (95–100)	99 (97–100)	0.51	0.56	0.58	0.26
Stroke*	95 (91–98)	99 (98–100)	97 (95–100)	0.02	0.006	0.2	0.1
Patients with NSTE-ACS							
MACE	85 (78–92)	84 (77–91)	91 (85–96)	0.31	0.89	0.21	0.14
All-cause death	92 (87–97)	90 (84–95)	94 (90–98)	0.51	0.49	0.66	0.25
ACS	94 (90–99)	95 (91–99)	98 (96–100)	0.29	0.76	0.12	0.2
Stroke	97 (94–100)	96 (92–100)	97 (94–100)	0.86	0.71	0.89	0.59

*Statistically significant (P<0.05 for overall comparison; P<0.016 for post hoc comparisons). Patients were divided into 3 time groups: T1 (August 2009–July 2012), T2 (August 2012–July 2015), and T3 (August 2015–July 2018). CI, confidence interval; MACE, major adverse cardiovascular events. Other abbreviations as in Table 1.

patients with STEMI are summarized in **Figure 3** and **Table 3**. Freedom from MACE was higher in the T3 than T1 and T2 groups (95% [95% CI 91–98%] vs. 87% [95% CI 83–92%] and 91% [95% CI 87–95%], respectively; P=0.057). There was a significant difference in freedom from MACE between the T1 and T3 groups (P=0.016). Freedom from all-cause death tended to be higher in the T3 than T1 and T2 groups (98 [96–100%] vs. 94% [91–98] and 93% [90–97], respectively; P=0.09).

Among patients with NSTE-ACS, freedom from MACE was comparable among the T1, T2, and T3 groups (85% [95% CI 78–92%] vs. 84% [95% CI 77–91%] vs. 91% [95% CI 85–96%], respectively; P=0.31; **Figure 4**; **Table 3**). The incidence of freedom from associated events was also comparable between the 3 groups.

Cause of Death

In total, 53 patients died within 2 years of discharge (18, 24, and 11 patients in the T1, T2, and T3 groups, respectively). The proportion of sudden deaths was comparable between the 3 groups (11%, 17%, and 9% in the T1, T2, and T3 groups, respectively). The proportion of cardiovascular deaths gradually decreased over time (39%, 33%, and 27% in the T1, T2, and T3 groups, respectively). The proportion of bleeding-related deaths was comparable among the 3 groups (6%, 8%, and 9% in the T1, T2, and T3 groups, respectively).

Incidence of Major Bleeding and Hospitalization for Heart Failure

Supplementary Figure 1 and **Table 4** show freedom from major bleeding in each of the groups. In the total ACS population, the incidence of major bleeding was lower in T1 than T2 and T3 groups (94% [95% CI 91–96%] vs. 97% [95% CI 94–98%] and 97% [95% CI 94–98%], respectively; P=0.19; **Table 4**). This tendency was more pronounced among patients with NSTE-ACS (incidence of major bleeding 90% [95% CI 85–96%] vs. 97% [95% CI 94–100%] and 97% [95% CI 93–100%] in the T1, T2, and T3 groups, respectively; P=0.058). Among patients with NSTE-ACS, the freedom from major bleeding tended to be higher in the T2 than T1 group (P=0.046). **Supplementary Figure 2** shows freedom from hospitalization for heart failure in each of the groups. In the total ACS population and in each of the subgroups, the incidence of hospitalization for heart failure was comparable among the groups.

Discussion

General Findings

The major findings of this study are as follows. First, the incidence of MACE was significantly lower in the T3 group than in the other 2 groups. This difference primarily originated from differences in all-cause death. Second, among patients with STEMI, the incidence of MACE was lower in the T3 group than in the other 2 groups. Third, among patients with NSTE-ACS, the incidence of MACE was comparable between the 3 groups. However, the incidence of major bleeding was significantly lower in the T3 group than in the T1 group.

Mid-Term Prognosis of AMI in the Current Clinical Settings

Previous studies using a real-world cohort demonstrated that guideline-recommended therapeutic management could have contributed to improving the prognostic outcomes for patients with AMI, particularly STEMI.[11,12] In attempts to adhere to the guideline-directed strategy, registry-based studies in developed countries have shown that the number of primary PCIs and the implementation of evidence-based medications (e.g., ASA, thienopyridine, ACEI/ARB, β-blockers, and statins) for patients with AMI increased over time from the 1990s to the 2000s.[4–6,13] Regarding data from the 2010s, several studies compared the temporal incidence of clinical events between the early

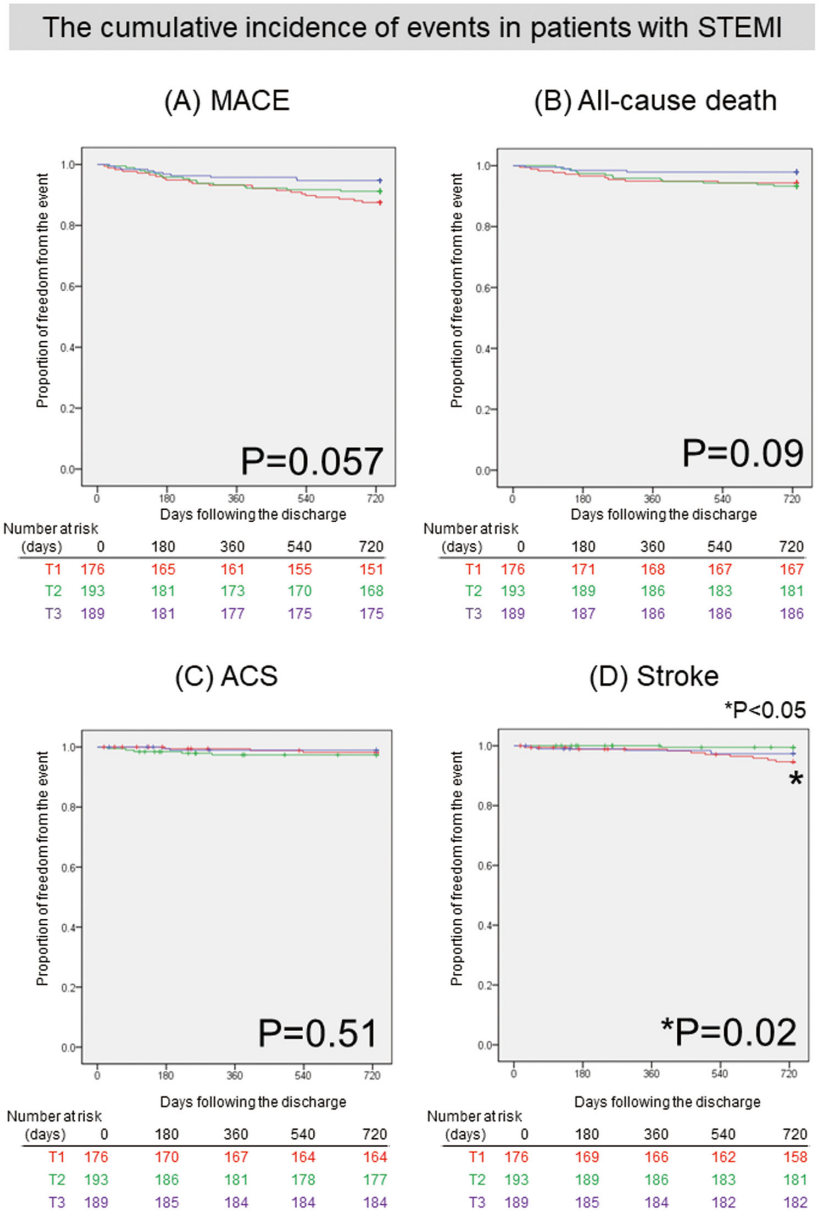

Figure 3. Cumulative incidence of clinical events in patients with ST-elevation myocardial infarction (STEMI) over time. (**A**) Freedom from major adverse cardiovascular events (MACE), (**B**) freedom from all-cause death, (**C**) freedom from recurrent of ACS, and (**D**) freedom from stroke. Patients were divided into 3 time groups: T1 (August 2009–July 2012; red), T2 (August 2012–July 2015; green), and T3 (August 2015–July 2018; purple). *Difference between groups (P<0.05).

2000s and 2010s.[4,5,14–16] The data commonly showed that the events associated with the coronary artery, such as recurrent AMI and stent thrombosis, were significantly decreased in cohorts from the early 2010s compared with those from the 2000s.[4,5,14–16] This difference may be due to advances in PCI technology, such as the implantation of DES, and the development of new-generation thienopyridine agents, because the incidence of such events would depend on the quality of the PCI and the regimen of antithrombotic therapy for secondary prevention.[4,15,16] However, few studies have compared the incidence of clinical events between the late 2010s and the prior periods. Puymirat et al compared the incidence of 6-month mortality in patients with AMI between 2015 and previous periods (e.g., 2010 and 2005) by analyzing a French multicenter registry.[5] In that study, 6-month mortality in patients with STEMI was lower in 2015 than in the other periods.[5] In the present study, our observation that the incidence of MACE in patients with ACS, particularly STEMI, was lower in the T3 group (2015–2018) than in previous periods (2009–2015) is in line with the results reported by Puymirat et al.[5] In addition, our finding that the incidence of all-cause death within 2 years was particularly improved in the T3 group also agreed with the findings of Puymirat et al.[5] Our findings could provide evidence for an improving mortality rate in patients with STEMI in the late 2010s. Regarding the mechanism, we inferred that the improvement in therapeutic management could have contributed to the reduction, rather than the change in patient demographics, because the fundamental characteristics of patients with STEMI remained generally unchanged during the study period. In addition, we previously reported that comor-

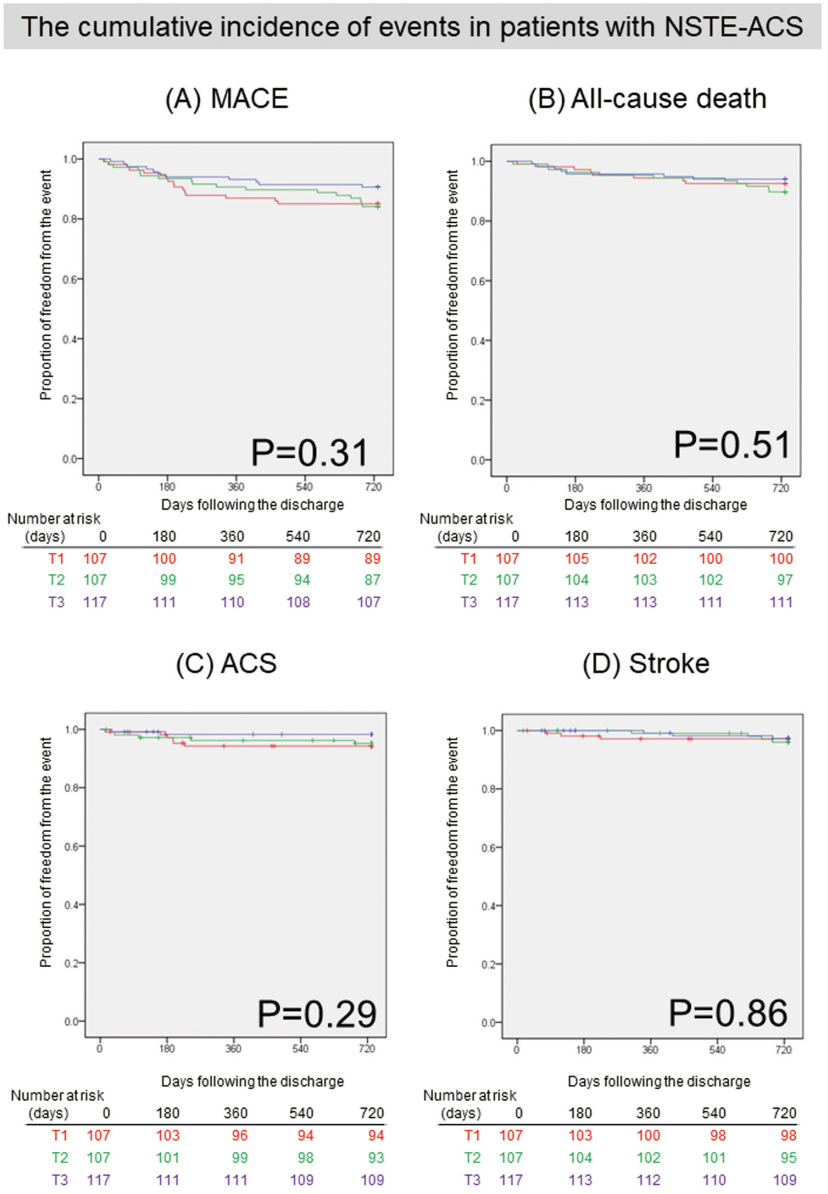

Figure 4. Cumulative incidence of clinical events in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) over time. (**A**) Freedom from major adverse cardiovascular events (MACE), (**B**) freedom from all-cause death, (**C**) freedom from recurrent of ACS, and (**D**) freedom from stroke. Patients were divided into 3 time groups: T1 (August 2009–July 2012; red), T2 (August 2012–July 2015; green), and T3 (August 2015–July 2018; purple).

Table 4. Cumulative Incidence of Freedom From Other Clinical Events in the Total ACS Population, in Patients With STEMI, and in Patients With NSTE-ACS Over Time

	Cumulative incidence (%) with 95% CI				P value (post hoc pairwise comparisons)		
	T1	T2	T3	P value	T1 vs. T2	T1 vs. T3	T2 vs. T3
Total ACS population							
Major bleeding	94 (91–96)	97 (94–98)	97 (94–98)	0.19	0.11	0.15	0.85
HF hospitalization	96 (94–98)	94 (92–97)	97 (95–99)	0.22	0.41	0.37	0.08
Patients with STEMI							
Major bleeding	96 (94–99)	97 (94–99)	97 (94–99)	0.98	0.85	0.88	0.97
HF hospitalization	97 (94–100)	94 (91–97)	97 (94–99)	0.3	0.18	0.86	0.22
Patients with NSTE-ACS							
Major bleeding	90 (85–96)	97 (94–100)	97 (93–100)	0.058	0.046	0.07	0.79
HF hospitalization	94 (90–99)	95 (91–99)	98 (96–100)	0.29	0.75	0.12	0.2

Patients were divided into 3 time groups: T1 (August 2009–July 2012), T2 (August 2012–July 2015), and T3 (August 2015–July 2018). HF, heart failure. Other abbreviations as in Tables 1,2.

bidities and therapeutic agents administered development of the event in patients with STEMI were relatively unchanged during the same study period.[7] Hence, we believe that factors regarding therapeutic management, such as the prevalence of relatively new therapeutic devices/agents, improved the incidence of MACE in patients with ACS, particularly STEMI, in the late 2010s. However, it remains unclear whether this phenomenon will be similarly observed in other regions. Further evaluations in different populations are warranted.

Clinical Implication

To our knowledge, this is the first study to conduct a temporal comparison of the incidence of mid-term prognostic events in patients who developed ACS between the late 2010s and prior periods in Japan. Previous studies comparing the incidence of clinical events between the mid-2000s and the early 2010s reported that the prognosis of patients with STEMI was unchanged or scarcely improved.[4,16] Compared with this previous population, our late 2010s population had a higher proportion of the use of conventional guideline-recommended agents, relatively new devices for PCI, and newly approved therapeutic agents.[4,16] Our data suggest that implementing guideline-directed management of ACS in current clinical settings could help to further improve the incidence of prognostic events in patients with STEMI.

We did not find an improvement in the incidence of clinical events in patients with NSTE-ACS in the late-2010s, although the incidence of major bleeding did decrease. Regarding NSTE-ACS, it may be challenging to improve the incidence of prognostic events because social and demographic factors (e.g., progression of an aging society and increase in comorbidities), as well as therapeutic management, are associated with its development.[7] Our data imply that further studies regarding the management of patients with NSTE-ACS are warranted to improve the incidence of prognostic events.

Study Limitations

Our study has several limitations. First, our data were collected from only 2 institutions in the same medical area. Hence, it remains unclear whether our data can be extrapolated to other medical areas in Japan and other countries. Second, because our data were collected retrospectively, unmeasured factors could have been missed. In particular, changes in environmental factors, such as the system for rapid reperfusion therapy and increased availability of bedside cardiac rehabilitation, could not be accounted for in our study design. Hence, we could not identify specific factors that may have contributed to the observed improvements. Third, therapeutic management of AMI continues to progress, even in contemporary clinical settings. For example, data for our population was collected in an era in which new strategies, such as short DAPT and aggressive lipid-lowering management, had not fully prevailed.[17,18] Fourth, our data show that in-hospital mortality was slightly higher and all-cause mortality after discharge was lower than in a previous study.[19] That is, the data could imply that patients with a severe status tend to die during hospitalization, which may make the mortality after discharge appear lower in our medical area. Moreover, most part of our study period was bofore the COVID-19 pandemic. During the pandemic, the incidence of clinical events, particularly hospitalization for heart failure, was affected by patients refraining from medical contact and unnecessary activities.[20] Hence, our data may not reflect therapeutic management in the latest clinical setting.

Conclusions

Our findings suggest that the incidence of mid-term MACE in patients who developed ACS during the late 2010s (2015–2018) was lower than that in prior periods (2009–2015). The difference originates from an improvement in the incidence of patients with STEMI.

Acknowledgment

The authors thank Hiromi Tokuda, Chief Medical Assistant at Shimane Prefectural Central Hospital, for collecting data.

Sources of Funding

This research did not receive any grant from any funding agency in the public, commercial, or not-for-profit sectors.

Disclosures

M. Yano, K.T. are members of *Circulation Reports*' Editorial Board. The remaining authors have no conflicts of interest to declare.

IRB Information

This study was performed in accordance with the Declaration of Helsinki and the ethical standards of the experimentations of both institutions. The study was approved by the institutional review boards of Shimane Prefectural Central Hospital (Churin R20-64) and Shimane University Hospital (2022206-1).

Data Availability

The deidentified participant data will not be shared.

References

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: Update from the GBD 2019 study. *J Am Coll Cardiol* 2020; **76:** 2982–3021.
2. Bertrand ME, Simoons ML, Fox KA, Wallentin LC, Hamm CW, McFadden E, et al. Management of acute coronary syndromes: Acute coronary syndromes without persistent ST-segment elevation. Recommendations of the Task Force of the European Society of Cardiology. *Eur Heart J* 2000; **221:** 1406–1432.
3. Ryan TJ, Anderson JL, Antman EM, Braniff BA, Brooks NH, Califf RM, et al. ACC/AHA guidelines for the management of patients with acute myocardial infarction: Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *Circulation* 1996; **94:** 2341–2350.
4. Szummer K, Wallentin L, Lindhagen L, Alfredsson J, Erlinge D, Held C, et al. Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: Experiences from the SWEDEHEART Registry 1995–2014. *Eur Heart J* 2017; **38:** 3056–3065.
5. Puymirat E, Simon T, Cayla G, Cottin Y, Elbaz M, Coste P, et al. Acute myocardial infarction: Changes in patient characteristics, management, and 6-month outcomes over a period of 20 years in the FAST-MI program (French registry of Acute ST-elevation or non-ST-elevation Myocardial Infarction) 1995–2015. *Circulation* 2017; **136:** 1908–1919.
6. Fox KA, Steg PG, Eagle KA, Goodman SG, Anderson FA, Granger CB, et al. Decline in rates of death and heart failure in acute coronary syndromes, 1996–2006. *JAMA* 2007; **297:** 1892–1900.
7. Ishiguchi H, Yasuda Y, Ishikura M, Yoshida M, Imoto K, Sonoyama K, et al. Trends over time in the incidences of ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction during the past decade in a rural Japanese high-aged population. *Circ J* 2021; **85:** 175–184.

8. Yasuda Y, Ishiguchi H, Ishikura M, Yoshida M, Imoto K, Sonoyama K, et al. Incidence and demographic trends for acute coronary syndrome in a non-epidemic area during the coronavirus disease pandemic in Japan: A 2-institutional observational study. *Circ Rep* 2021; **3:** 95–99.
9. Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, et al. Universal definition of myocardial infarction. *Circulation* 2007; **116:** 2634–2653.
10. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: A consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011; **123:** 2736–2747.
11. Nallamothu BK, Normand ST, Wang Y, Hofer TP, Brush JE, Messenger JC, et al. Relation between door-to-balloon times and mortality after primary percutaneous coronary intervention over time: A retrospective study. *Lancet* 2015; **385:** 1114–1122.
12. Wada H, Ogita M, Suwa S, Nakao K, Ozaki Y, Kimura K, et al. Guideline adherence and long-term clinical outcomes in patients with acute myocardial infarction: A Japanese registry of acute myocardial infarction diagnosed by universal definition (J-MINUET) substudy. *Eur Heart J Acute Cardiovasc Care* 2020; **9:** 939–947.
13. Rogers WJ, Frederick PD, Stoehr E, Canto JG, Ornato JP, Gibson CM, et al. Trends in presenting characteristics and hospital mortality among patients with ST elevation and non-ST elevation myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. *Am Heart J* 2008; **156:** 1019–1022.
14. Krumholz HM, Normand ST, Wang Y. Twenty-year trends in outcomes for older adults with acute myocardial infarction in the United States. *JAMA Netw Open* 2019; **2:** e191938, doi:10.1001/jamanetworkopen.2019.1938.
15. Takeji Y, Shiomi H, Morimoto T, Yoshikawa Y, Taniguchi R, Mutsumura-Nakano Y, et al. Demographics, practice patterns and long-term outcomes of patients with non-ST-segment elevation acute coronary syndrome in the past two decades: The CREDO-Kyoto Cohort-2 and Cohort-3. *BMJ Open* 2021; **11:** e044329, doi:10.1136/bmjopen-2020-044329.
16. Takeji Y, Shiomi H, Morimoto T, Yoshikawa Y, Taniguchi R, Mutsumura-Nakano Y, et al. Changes in demographics, clinical practices and long-term outcomes of patients with ST segment-elevation myocardial infarction who underwent coronary revascularization in the past two decades: Cohort study. *BMJ Open* 2021; **11:** e043683, doi:10.1136/bmjopen-2020-043683.
17. Kedhi E, Fabris E, van der Ent M, Buszman P, von Birgelen C, Roolvink V, et al. Six months versus 12 months dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction (SAPT-STEMI): Randomized, multicenter, non-inferiority trial. *BMJ* 2018; **363:** k3793, doi:10.1136/bmj.k3793.
18. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018; **379:** 2097–2107.
19. Yasuda S, Nakao K, Nishimura K, Miyamoto Y, Sumita Y, Shindo T, et al. The current status of cardiovascular medicine in Japan: Analysis of a large number of health records from a nationwide claim-based database, JROAD-DPC. *Circ J* 2016; **80:** 2327–2335.
20. Andersson C, Gerds T, Fosbøl E, Phelps M, Andersen J, Lamberts M, et al. Incidence of new-onset and worsening heart failure before and after COVID-19 epidemic lockdown in Denmark: A nationwide cohort study. *Circ Heart Fail* 2020; **13:** e007274, doi:10.1161/CIRCHEARTFAILURE.120.007274.

Supplementary Files

Please find supplementary file(s);
https://doi.org/10.1253/circrep.CR-23-0029