In-Hospital Outcomes After Percutaneous Coronary Intervention for Acute Coronary Syndrome With Cardiogenic Shock (from a Japanese Nationwide Registry [J-PCI Registry])

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In-hospital complications and their predictors in acute coronary syndrome (ACS) patients with cardiogenic shock (CS) have not been fully investigated, particularly in those who underwent invasive revascularization procedures. This study investigated the in-hospital outcomes, along with the volume-outcome relationship of ACS patients with CS, using a contemporary large-scale nationwide percutaneous coronary intervention (PCI) registry in Japan. We analyzed PCI procedural data on ACS patients treated between 2014 and 2016 in a nationwide Japanese PCI registry. Predictors of in-hospital death and major bleeding complications requiring transfusion were identified via multivariable logistic regression analysis. The association of bleeding complications with in-hospital death was also analyzed. This study enrolled 253,355 patients who underwent PCI for ACS, of whom 17,549 (6.9%) were with CS. The rates of in-hospital mortality and access/nonaccess site bleeding complications in CS patients were 13.2%, 1.2%, and 1.3%, respectively. Age, gender, and baseline kidney condition, along with presentation status (e.g., cardiopulmonary arrest and/or acute heart failure) or the number and location of diseased vessels (e.g., left main lesion), were associated with in-hospital mortality and bleeding complications. Of note, the in-hospital mortalities decreased in parallel with the increasing institutional PCI volumes. In-hospital mortality also differed by the presence of concomitant bleeding complications (43.1% and 48.3% with access or nonaccess site bleeding, and 12.9% and 12.7% without, respectively). In conclusion, in-hospital mortality was 13.2% in ACS patients with CS who underwent contemporary PCI. Other than traditional predictors of PCI complications, lower institutional PCI volumes, and concurrent bleeding were associated with higher in-hospital mortality. **© 2019 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2019;123:1595−1601)**

Mortality in acute coronary syndrome (ACS) patients complicated by cardiogenic shock (CS) remains high.[1−3] Previous small studies have demonstrated that patient background information such as age, diabetes mellitus, renal dysfunction, and left main disease was associated with higher mortality.[4,5] In addition, periprocedural complications can affect the outcome of CS patients. In particular, bleeding complications are well known as a poor prognostic factor after percutaneous coronary intervention (PCI).[6,7] CS patients have a high rate of bleeding complications,[8,9] and both access site and nonaccess site bleeding can lead to hemodynamic instability and poor outcomes. However, the incidence, predictors, and clinical impact of bleeding events in patients after PCI for ACS with CS have not been well evaluated in a large-scale study to date. The purposes of the present study were (1) to investigate the incidence and determinants of in-hospital death and bleeding complications, and (2) to evaluate the impact of the access site and nonaccess site bleeding on in-hospital mortality using a contemporary nationwide Japanese PCI (J-PCI) registry.

Methods

The J-PCI registry is an ongoing, prospective, and multicenter Japanese nationwide PCI registry conducted by the Japanese Association of Cardiovascular Intervention and Therapeutics (CVIT), which has been designed to collect data on clinical backgrounds and in-hospital outcomes of patients who underwent PCI.[10−13] Since 2013, the J-PCI

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registry has been incorporated into the National Clinical Data system, a nationwide prospective web-based registration system. A data manager in each hospital is responsible for collecting PCI data and submitting them to the dedicated online database. The CVIT has an annual meeting of data managers to ensure proper data collection and performs random site visits to validate the submitted data. In this study, we analyzed PCI procedural data on ACS patients treated between 2014 and 2016 in this registry. ACS included ST elevation myocardial infarction and non-ST elevation myocardial infarction or unstable angina (non-ST elevation ACS).

The definitions of respective variables are available online (http://www.cvit.jp/registry/jpci_definition.pdf; written in Japanese). In brief, CS was defined as an episode of systolic blood pressure <80 mm Hg, cardiac index <1.8 L/min/m^2, and/or the requirement for parenteral inotropic or vasopressor agents or mechanical support to maintain blood pressure and cardiac indexes above those levels. Acute myocardial infarction was defined as sustained symptoms suggesting myocardial ischemia and detection of an increase in cardiac biomarker values (creatine phosphokinase and/or creatine phosphokinase myocardial band isoform levels above twice the normal limit and/or cardiac troponin levels above the Ninety-ninth percentile cut-off point). ST and non-ST elevation myocardial infarction was defined as myocardial infarction with and without ST elevation seen on electrocardiogram. Unstable angina was defined as ACS without any findings of myocardial infarction. In-hospital outcomes in this registry included in-hospital (either until discharge or within 30 days after PCI) death, procedure-related myocardial infarction, cardiac tamponade, stent thrombosis, emergent cardiac surgery, and major bleeding complications. Procedure-related myocardial infarction was defined as elevation of cardiac troponin 5-fold above ninety-ninth percentile upper reference limit occurring within 48 hours of the procedure.[14] Cardiac tamponade was defined as new pericardial effusion which worsens hemodynamics after PCI. Stent thrombosis was defined as definite stent thrombosis according to Academic Research Consortium definition.[15] Major bleeding complications in access and nonaccess sites were defined as perioperative and/or postoperative bleeding requiring blood transfusion, including access site and nonaccess site bleeding. In a total of 1019 institutions, institutional volume was categorized as the first quartile (<640 cases/ 3 years), second quartile (640 to 968 cases/ 3 years), third quartile (969 to 1490 cases/3 years), and fourth quartile (>1490 cases/3 years) institutions from low volume institutions to high volume institutions according to the total number of PCI procedures between January 2014 and December 2016.

Categorical variables were reported as numbers with relative percentage and compared using the chi-square test. Continuous variables were expressed as mean ± standard deviation and were compared using unpaired Student's *t* test or the Mann-Whitney *U* test as appropriate. The Cochran-Armitage analysis was used to evaluate the trend of the in-hospital mortality in the institutional volume categories. Multivariable logistic regression analysis was performed to identify the independent predictors of in-hospital death and access site and nonaccess site bleeding events in ACS patients with CS. Variables entered into these multivariable analyses included age, male gender, hypertension, diabetes, dyslipidemia, current smoker, long-term kidney disease, hemodialysis, history of PCI, history of cardiac bypass grafting surgery, history of heart failure, history of myocardial infarction, peripheral artery disease, long-term occlusive pulmonary disease, ST elevation myocardial infarction, cardiac arrest within 24 hours, acute heart failure within 24 hours, radial access PCI, number of diseased vessels, left main disease, and institutional volume. We also included institutions as a random intercept. Odds ratio and 95% confidence intervals were reported. Patients with missing values were excluded from the multivariable analyses. Two-sided p values <0.05 were considered significant. All data were analyzed using the R statistical software version 3.5.1 (Free Software Foundation, Inc, Boston, Massachusetts).

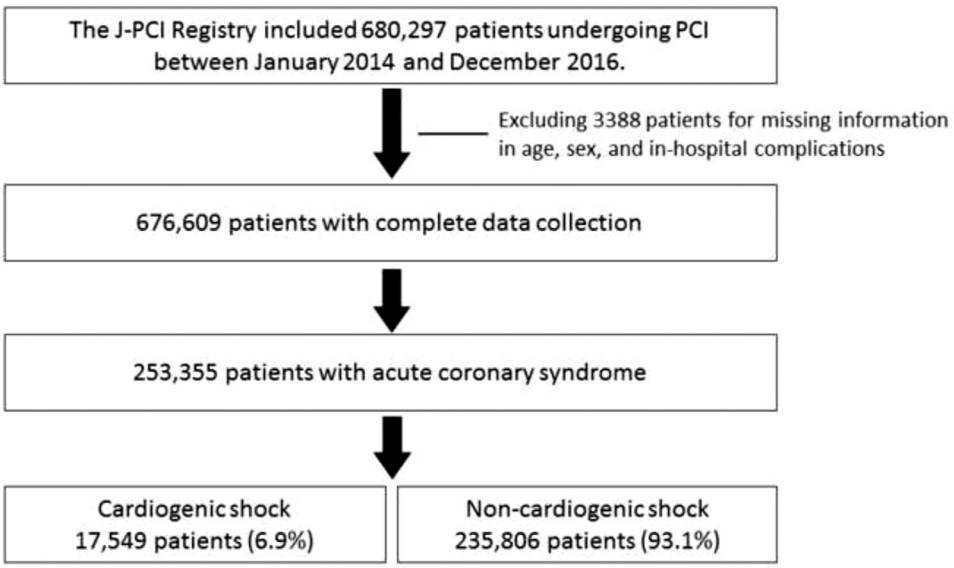

Figure 1. Study flow chart.
PCI = percutaneous coronary intervention.

Table 1
Baseline characteristics of ACS patients with and without CS

	Cardiogenic shock		p value
	Yes	No	
Variable	(n = 17546)	(n = 235806)	
Age (years)	70.8 ± 12.4	69.3 ± 12.2	<0.001
Men	13012 (74%)	177033 (75%)	0.007
Hypertension	11181 (70%)	167226 (75%)	<0.001
Diabetes mellitus	7018 (44%)	89057 (40%)	<0.001
Dyslipidemia	8531 (53%)	141737 (64%)	<0.001
Current smoker	5861 (37%)	82315 (37%)	0.46
Chronic kidney disease	4265 (27%)	32848 (15%)	<0.001
Hemodialysis	929 (5.8%)	10350 (4.6%)	<0.001
Prior PCI	3305 (19%)	69292 (29%)	<0.001
Prior CABG	592 (3.4%)	6524 (2.8%)	<0.001
Prior heart failure	2685 (16%)	21489 (9.2%)	<0.001
Prior myocardial infarction	2832 (16%)	39162 (17%)	0.37
Chronic obstructive pulmonary disease	435 (2.7%)	4358 (2.0%)	<0.001
Peripheral artery disease	435 (2.7%)	4358 (2.0%)	<0.001
Clinical presentation			<0.001
ST elevation myocardial infarction	13727 (78%)	105789 (45%)	
Non-ST elevation ACS	3822 (22%)	130017 (55%)	
Cardiopulmonary arrest	6839 (39%)	2047 (0.87%)	<0.001
Acute heart failure	10788 (62%)	11112 (4.7%)	<0.001
Access site			<0.001
Femoral access	12373 (71%)	82627 (35%)	
Radial access	4367 (25%)	143289 (61%)	
Number of narrowed coronary arteries			<0.001
1	7162 (41%)	135928 (58%)	
2	4282 (24%)	60557 (26%)	
3	3545 (20%)	30535 (13%)	
Left main narrowed	2560 (15%)	8786 (3.7%)	<0.001
Target coronary artery			
Right	7497 (43%)	83488 (35%)	<0.001
Left main-left anterior descending	10229 (58%)	123748 (54%)	<0.001
Left circumflex	3993 (23%)	54176 (23%)	0.51
Bypass graft	110 (0.63%)	1151 (0.49%)	0.01
Institutional volume (according to the number of PCI cases)			<0.001
1st quartile	4970 (28%)	65890 (28%)	
2nd quartile	4638 (26%)	59158 (25%)	
3rd quartile	5158 (29%)	60743 (26%)	
4th quartile	2783 (16%)	50015 (21%)	

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; CS = cardiogenic shock; PCI = percutaneous coronary intervention.

Results

The J-PCI registry contains 680,297 patients who underwent PCI between January 2014 and December 2016. We excluded 3,388 patients for missing information such as age, gender, and in-hospital complications. Of the remaining 676,609, 253,355 patients who underwent PCI for ACS were included in this study. Of them, 17,549 patients (6.9%) were with CS and 235,806 (93.1%) were without CS. The study flow chart is shown in Figure 1. The baseline patient characteristics in ACS patients with and without CS are shown in Table 1.

In-hospital outcomes in ACS patients with and without CS are demonstrated in Table 2. In a volume-outcome analysis, the in-hospital mortalities decreased in parallel with the increasing institutional PCI volumes (p for trend = 0.01) (Figure 2). A multivariable logistic regression model for the predictors of in-hospital death in ACS patients with CS is shown in Table 3. The most powerful predictor was cardiopulmonary arrest before PCI, followed by acute heart failure before PCI, left main coronary artery disease, non-ST elevation ACS, and radial access. The higher PCI volume institutions were also associated with a lower in-hospital mortality.

The predictors of access and nonaccess site bleeding complications in ACS patients with CS are shown in Table 4. Among predictors of such complications, age, gender, long-term kidney disease, cardiopulmonary arrest, acute heart failure, access site, number of diseased vessels, and left main coronary artery disease were common predictors of in-hospital mortality. Notably, radial access was independently associated with not only access site bleeding (odds ratio 0.23, 95% confidence intervals 0.18 to 0.29, p <0.001) but also nonaccess site bleeding (odds ratio 0.64, 95% confidence intervals 0.52 to 0.79, p <0.001).

Regarding the impact of bleeding complications on in-hospital mortality, the in-hospital mortality was 43.1% in patients with access site bleeding, 48.3% in those with nonaccess site bleeding, 12.9% in those without access site bleeding, and 12.7% in those without nonaccess site bleeding, respectively (Figure 3). The in-hospital mortality was similar between the radial and femoral accesses in both patients with access site complications and those with nonaccess site bleeding complications, but was significantly lower in the radial access than in the femoral access in patients without the access and nonaccess site bleeding complications (Figure 4).

Discussion

The salient findings of the present study are as follows:[1] the in-hospital mortality in ACS patients with CS who underwent PCI was 13.2% in the largest nationwide multicenter registry in Japan[2]; traditional patient background predictors of adverse PCI outcome (e.g., age, gender, and baseline kidney condition), along with urgent clinical presentation (e.g., cardiopulmonary arrest and/or acute heart failure within 24 hours) and angiographic characteristics (e.g., number of diseased vessels, and left main coronary artery disease) were associated with both in-hospital mortality and bleeding complications, and not surprisingly, CS patients experiencing bleeding events had extremely high mortality rates; and[3] the in-hospital mortalities decreased in parallel with the increasing institutional PCI volumes.

In data on the Western countries, mortality rates of CS patients who underwent coronary revascularization have been reported to be 30% to 40%.[4,16,17] In this study, the in-hospital mortality of CS patients was relatively low (13.2%). Previous registries included CS patients with "persistent (>30 minutes or 60 minutes)" hypotension or low cardiac index, and the incidence of CS has been reported to be approximately 4% in ACS patients.[4,16,17] In the J-PCI registry, CS was defined as "an episode" of hypotension or low cardiac index, and the incidence of CS was 6.9%. Because

Table 2
In-hospital outcomes in ACS patients with and without CS

	Cardiogenic shock		p value
	Yes	No	
Variable	(n = 17546)	(n = 235806)	
In-hospital mortality	2319 (13%)	1653 (0.70%)	<0.001
Cardiac tamponade	121 (0.69%)	321 (0.14%)	<0.001
Stent thrombosis	169 (0.96%)	604 (0.26%)	<0.001
Emergent surgery	129 (0.74%)	281 (0.12%)	<0.001
Bleeding complications	420 (2.4%)	790 (0.34%)	<0.001
Access site bleeding	211 (1.2%)	454 (0.19%)	<0.001
Nonaccess site bleeding	230 (1.3%)	352 (0.15%)	<0.001

ACS = acute coronary syndrome; CS = cardiogenic shock.

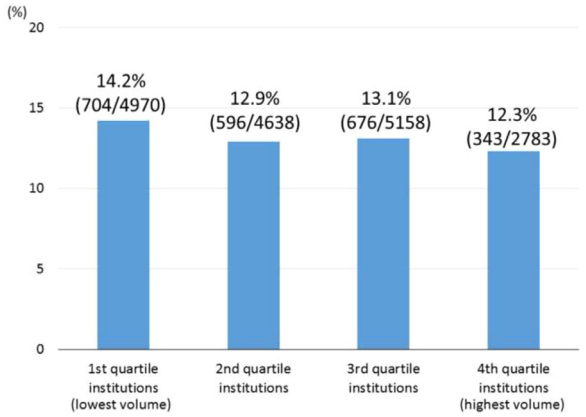

Figure 2. In-hospital mortality in CS patients according to institutional PCI volume.
CS = cardiogenic shock, PCI = percutaneous coronary intervention.

Table 3
Multivariable logistic regression model for in-hospital death in ACS patients with CS

Variables	OR	95% CI	p value
Age (1-year increase)	1.04	1.03-1.04	<0.001
Male sex	0.83	0.76-0.91	<0.001
Hypertension	0.82	0.75-0.89	<0.001
Diabetes mellitus	1.16	1.07-1.25	<0.001
Dyslipidemia	0.60	0.56-0.65	<0.001
Current smoker	0.78	0.71-0.86	<0.001
Chronic kidney disease	1.62	1.47-1.78	<0.001
Hemodialysis	1.11	0.95-1.30	0.17
Prior PCI	0.83	0.74-0.93	0.002
Prior CABG	0.98	0.80-1.20	0.84
Prior heart failure	1.30	1.17-1.46	<0.001
Prior myocardial infarction	1.24	1.09-1.40	0.001
Chronic obstructive pulmonary disease	1.37	1.11-1.70	0.004
Peripheral artery disease	1.33	1.16-1.54	<0.001
Non-ST elevation ACS	0.39	0.36-0.43	<0.001
Cardiopulmonary arrest	7.40	6.72-8.15	<0.001
Acute heart failure	4.50	4.12-4.92	<0.001
Radial artery access	0.41	0.37-0.45	<0.001
Number of narrowed coronary artery			
1	Reference		
2	1.11	1.001-1.22	0.049
3	1.78	1.60-1.97	<0.001
Left main narrowed	2.99	2.65-3.37	<0.001
Institutional volume (quartile)			
1st	Reference		
2nd	0.74	0.59-0.92	0.007
3rd	0.83	0.65-1.06	0.13
4th	0.68	0.50-0.93	0.02

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; CI = confidence intervals; CS = cardiogenic shock; OR = odds ratio; PCI = percutaneous coronary intervention.

the duration and situation of hypotension are uncertain in some patients, we applied this definition to collect every CS patient in Japan. However, our definition is different from the global standard definition, and needs to be assessed in the future studies. In addition, culprit lesions might have affected the results. A previous study showed that the prevalence of left main and left anterior descending coronary artery disease in CS patients was more than 90%,[17] whereas that in this study was 58%. Left main and left anterior descending arteries related to CS have been reported to have poorer clinical outcomes than right coronary arteries related to CS.[18] Therefore, inclusion of less severe CS patients may have led to the low in-hospital mortality in this study.

In-hospital mortality risk in patients with bleeding complications was more than 3 times greater than that in those without bleeding complications. A previous meta-analysis reported that the hazard ratio of access and nonaccess site bleeding on 1-year mortality in patients with ST elevation myocardial infarction was 1.2 and 1.6, respectively.[19] Bleeding complications in CS patients seem to lead to a greater risk of death compared with those in non-CS patients. Prevention and management of bleeding complications can improve the clinical outcomes of ACS patients with CS. Among the predictors of access and nonaccess site bleeding complications, the choice of access site may be important to prevent the bleeding complications. One of the main clinical features of this study was the high frequency of radial access PCI (25%) even for ACS patients with CS in contrast with only 4% in a US registry.[17] Some small studies and a meta-analysis supported the superiority of radial access to reduce mortality and bleeding complications even in cases requiring mechanical support device.[20,21] Furthermore, in cases requiring mechanical support device, radial access PCI has been reported to be associated with favorable clinical outcomes due to less access site bleeding.[22] If radial arteries are weakly palpable, radial artery puncture could be feasible option in patients with CS.[20] In our study, radial access was strongly associated with a lower risk of bleeding complications, suggesting that it may be a preferable access site even in the setting of CS when technically possible without delay in obtaining the PCI access.

In the institutional volume analysis, there were declining trends in the in-hospital mortality and access site bleeding events from the low volume to high volume institutions. Previous studies showed that institutional PCI volume was inversely associated with adverse events in patients with both stable coronary artery disease and acute myocardial infarction.[12,23] High volume centers may have sufficient staff members for multidisciplinary teams, experiences, and established systems for CS patients' management, and subsequently have less in-hospital events. While tertiary

Table 4
Multivariable logistic regression model for access site and nonaccess site bleeding complications in ACS patients with CS

Variables	Access site bleeding		p value	Nonaccess site bleeding		p value
	OR	95% (CI)		OR	95% (CI)	
Age (1-year increase)	1.03	1.02-1.03	<0.001	1.03	1.02-1.04	<0.001
Male sex	0.38	0.32-0.46	<0.001	0.66	0.54-0.80	<0.001
Hypertension	1.08	0.88-1.32	0.45	1.03	0.83-1.28	0.77
Diabetes mellitus	0.81	0.69-0.96	0.02	0.90	0.75-1.08	0.26
Dyslipidemia	0.97	0.82-1.15	0.76	0.87	0.72-1.05	0.14
Current smoker	0.89	0.71-1.10	0.27	0.997	0.80-1.24	0.98
Chronic kidney disease	1.33	1.08-1.63	0.007	1.64	1.32-2.04	<0.001
Hemodialysis	1.32	0.97-1.79	0.08	1.23	0.87-1.75	0.25
Prior PCI	0.84	0.67-1.06	0.14	0.83	0.63-1.08	0.16
Prior CABG	1.31	0.97-1.88	0.14	1.09	0.69-1.73	0.71
Prior heart failure	1.10	0.87-1.39	0.41	1.20	0.92-1.55	0.18
Prior myocardial infarction	1.14	0.88-1.47	0.32	0.93	0.69-1.25	0.63
Chronic obstructive pulmonary disease	1.17	0.70-1.96	0.55	1.25	0.76-2.04	0.38
Peripheral artery disease	0.98	0.72-1.35	0.92	1.28	0.92-1.77	0.15
Non-ST elevation ACS	0.94	0.78-1.12	0.47	0.66	0.54-0.81	<0.001
Cardiopulmonary arrest	3.11	2.43-3.97	<0.001	3.43	2.68-4.39	<0.001
Acute heart failure	1.63	1.32-2.02	<0.001	3.02	2.42-3.77	<0.001
Radial artery access	0.23	0.18-0.29	<0.001	0.64	0.52-0.79	<0.001
Number of narrowed coronary artery						
1	Reference			Reference		
2	1.44	1.17-1.77	<0.001	1.22	0.97-1.52	0.09
3	1.59	1.26-2.02	<0.001	1.34	1.03-1.73	0.03
Left main narrowed	3.14	2.44-4.04	<0.001	2.87	2.20-3.76	<0.001
Institutional volume (quartile)						
1st	Reference			Reference		
2nd	0.89	0.67-1.18	0.41	1.03	0.72-1.46	0.88
3rd	0.72	0.53-0.98	0.04	0.79	0.54-1.17	0.24
4th	0.69	0.47-0.99	0.046	0.78	0.49-1.25	0.30

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; CI = confidence intervals; CS = cardiogenic shock; OR = odds ratio; PCI = percutaneous coronary intervention, .

high volume centers should be a cardiogenic shock center,[24] it is a matter of debate whether centralization of CS patients to the high-volume centers overcomes the risk of delay in treating ACS patients complicated with CS.

The present study had several limitations. First, some important variables for CS patients, such as mechanical support device, antiplatelet therapy regimen, and door-to-balloon time, were not available in this study. Notably, mechanical support device insertion can largely affect the in-hospital mortality and bleeding complications. In patients treated by radial access PCI requiring mechanical support devices, femoral access may be additionally obtained. The absence of mechanical support device data possibly distorted the analysis of radial versus femoral access. However, because mechanical support devices did not show the survival benefit in several randomized control trials,[25,26] the lack of data on mechanical support device might not have a critical impact on our results. Furthermore, the median door-to-balloon time was 40 to 90 minutes in Japanese registries,[27,28] and is not different from that of a National PCI registry in the U.S. (85 minutes in 2005 and 63 minutes in 2011).[29] Second, the choice of access site in clinical practice tended to depend on the hemodynamic instability. Because radial access is likely to be selected in less severe CS patients, it can result in the lower mortality even in patients without access and nonaccess site bleeding. This selection bias may be associated with a lower in-hospital mortality rate in patients treated with radial access, and the results of this study should be interpreted considering this important limitation. Third, some in-hospital events have been possibly missed to be registered. Fourth, the definition of bleeding complications in this study was not based on standardized definitions. Therefore, the actual incidence of bleeding complications may be underestimated. Finally, the

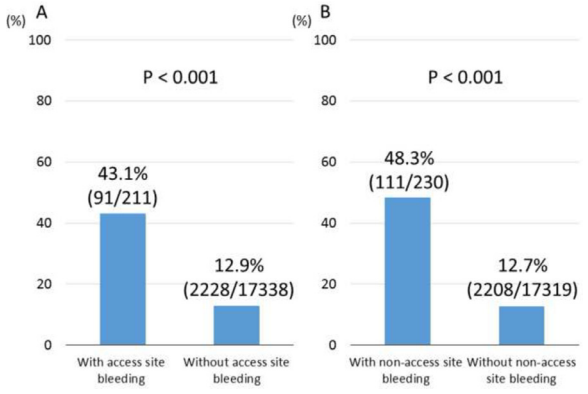

Figure 3. In-hospital mortality in CS patients with and without bleeding complications.
In-hospital mortality in CS patients with and without access site bleeding complications (*A*) and with and without nonaccess site bleeding complications (*B*).
CS = cardiogenic shock.

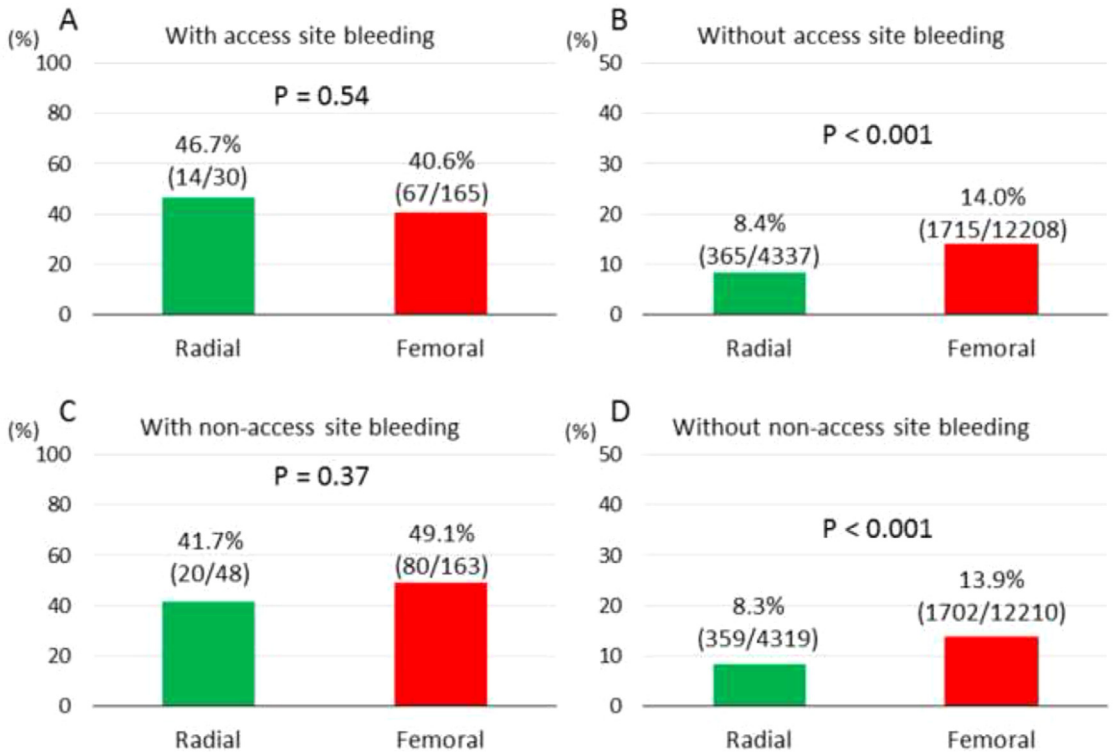

Figure 4. In-hospital mortality in CS patients with and without bleeding complications according to approach sites.
In-hospital mortality in CS patients who underwent PCI through radial and femoral accesses with access site bleeding (*A*), without access site bleeding (*B*), with nonaccess site bleeding (*C*), and without nonaccess site bleeding (*D*).
CS = cardiogenic shock, PCI = percutaneous coronary intervention.

details of bleeding complications were not recorded in the J-PCI registry.

In conclusion, in-hospital mortality was 13.2% in ACS patients with CS who underwent contemporary PCI. Other than traditional predictors of PCI complications, lower institutional PCI volumes and concurrent bleeding were associated with higher in-hospital mortality.

Disclosures

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