Table 2. Predictors of Use of DAPT

	OR	95% CI	P value
Age 60–69 years	1.57	1.37–1.80	<0.001
Age 70–79 years	1.58	1.37–1.82	<0.001
Age >80 years	1.54	1.27–1.86	<0.001
Female	0.84	0.73–0.97	0.017
BMI	1.12	1.02–1.22	0.013
Hypertension	1.25	1.10–1.42	<0.001
Hyperlipidemia	1.47	1.31–1.66	<0.001
Smoking	1.21	1.07–1.37	0.002
CKD stage ≥3	1.35	1.11–1.64	0.003
Without ischemic symptoms	1.34	1.12–1.62	0.002
Prior CABG	0.57	0.43–0.77	<0.001
CCS class 4	0.71	0.59–0.85	<0.001
HF	0.60	0.50–0.71	<0.001
Therapy for angina pectoris	1.22	1.03–1.44	0.022
Urgent PCI	1.17	1.04–1.33	0.011
3-vessel disease	1.25	1.09–1.45	0.002

CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

Table 3. Outcomes According to Use of Preprocedural Antiplatelet Therapy

	Non-DAPT (n=2,079), % (n)	DAPT (n=4,449), % (n)	P value
Death, shock, HF	5.1 (105)	3.3 (146)	0.001
Death	1.3 (28)	1.1 (49)	0.392
Shock	2.3 (48)	1.6 (69)	0.032
HF	2.9 (61)	1.5 (67)	<0.001
Coronary dissection	1.3 (28)	1.1 (51)	0.490
Coronary perforation	0.9 (19)	1.0 (43)	0.838
Cerebral infarction	0.6 (13)	0.3 (15)	0.097
Cerebral bleeding	0.0 (1)	0.0 (1)	0.582
Cardiac tamponade	0.3 (7)	0.3 (14)	0.884
HD introduction	1.3 (27)	0.4 (19)	<0.001
Thrombosis	0.0 (0)	0.1 (6)	0.094
Blood transfusion	1.9 (39)	1.6 (73)	0.496
Bleeding <72 h			
Puncture site	0.8 (16)	0.9 (38)	0.725
Hematoma	0.8 (17)	1.0 (45)	0.452
Retroperitoneal hemorrhage	0.0 (1)	0.0 (2)	0.956
Gastrointestinal bleeding	0.4 (9)	0.2 (11)	0.206
Urological bleeding	0.1 (2)	0.1 (5)	0.852
Other bleeding	0.9 (18)	0.7 (31)	0.461
Postprocedural MI	38.1 (622)	28.7 (1,167)	<0.001

HD, hemodialysis. Other abbreviations as in Table 1.

Japanese PCI registry-based study and evaluated the effect of DAPT on in-hospital outcomes, including PCI-related MI.

Methods

Study Design

The Japan Cardiovascular Database Keio interhospital Cardiology Study (JCD-KiCS) is a large, ongoing, prospective, multicenter registry that contains the clinical background and outcome data (approximately 200 variables) from consecutive PCI cases.[14–17] Participating hospitals were instructed to record data from consecutive hospital visits for patients undergoing PCI using any commercially available coronary device and to register the data in an internet database. The information was tracked by the site investigator and by the responsible coordinators. The database system was checked to ensure that the reported data were complete and internally consistent. The decision to perform PCI was made according to the investigators' clinical assessment of the patient. The study did not mandate specific interventional or surgical techniques such as vascular access or use of specific stents or closure devices.

The majority of the clinical variables in the JCD were defined according to the National Cardiovascular Data Registry (NCDR). The NCDR is a large PCI registry system, sponsored by the American College of Cardiology, with more than 1,000,000 entries related to ischemic heart disease and more

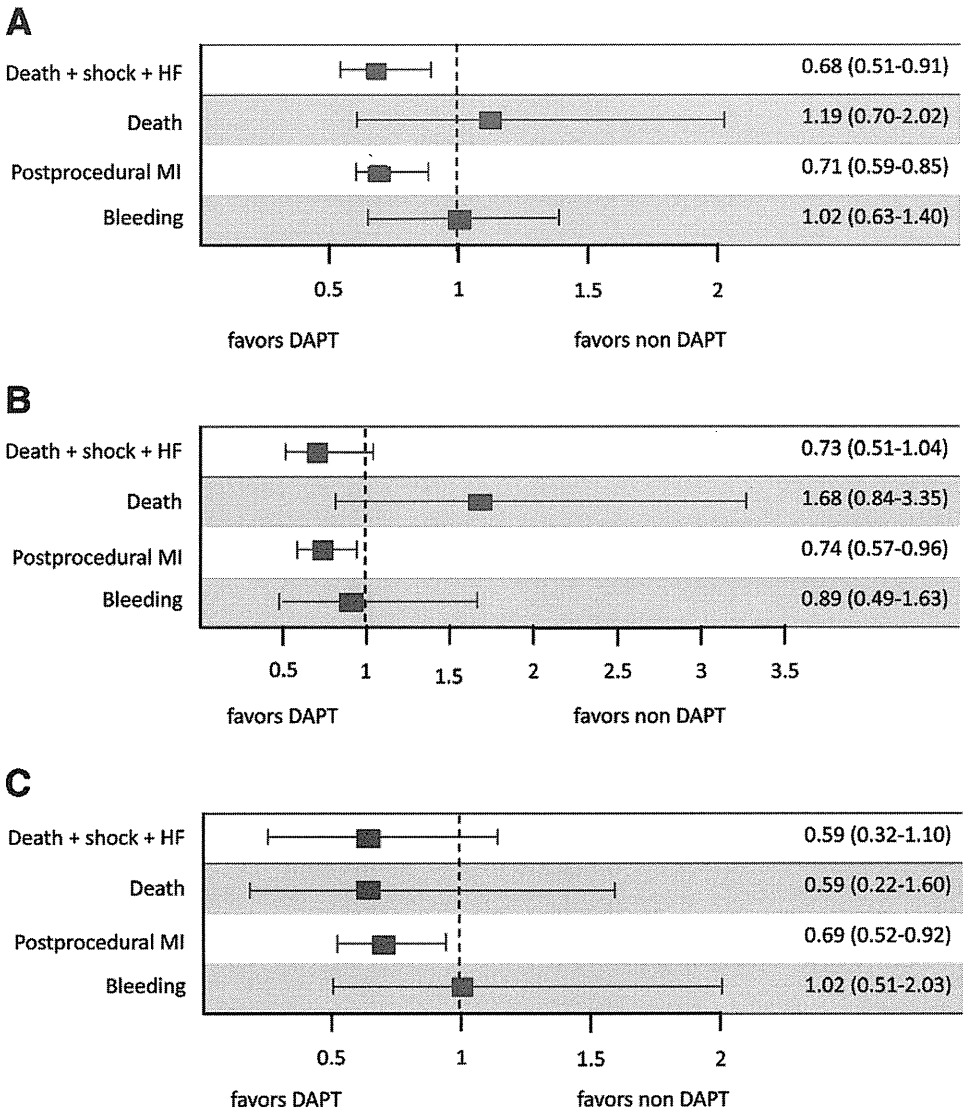


Figure. (**A**) Adjusted in-hospital outcomes. Forest plot of odds ratios (ORs) and 95% confidence intervals (CIs) for in-hospital outcomes among patients who did or did not undergo dual antiplatelet therapy (DAPT) before percutaneous coronary intervention (PCI). (**B**) Adjusted in-hospital outcomes in ST-elevation MI (STEMI) patients. Forest plot of ORs and 95% CIs for in-hospital outcomes among STEMI patients who did or did not undergo DAPT before PCI. (**C**) Adjusted in-hospital outcomes in non-ST-elevation (NSTE)-acute coronary syndrome (ACS) patients. Forest plot of ORs and 95% CIs for in-hospital outcomes among NSTE-ACS patients who did or did not undergo DAPT before PCI. HF, heart failure; MI, myocardial infarction.

than 500,000 entries for PCI collected from more than 500 institutions in the USA.[18] The variables were compared to determine the factors that lead to disparities in PCI management.

Patients who received aspirin and clopidogrel within 24h before the procedure were defined as DAPT users. Patients with clinical contraindications for DAPT therapy were excluded from the current analysis. In this study, we focused on clopidogrel and excluded other antiplatelet combinations such as cilostazol or ticlopidine. In Japan, the approved loading dose of clopidogrel is 300mg and therefore it was the only dose provided to the patients in this registry.[19] Prasugrel and ticagrelor were not approved at the time of this analysis. In Japan, the recommended loading dose of aspirin is 162–325mg.[7,8] Patients did not receive GP IIb/IIIa inhibitors, as they were not approved in Japan at the time of this study. In a randomized clinical trial, the efficacy of abciximab in preventing post-PCI coronary events in Japanese patients was not detected, and the incidence of bleeding complications tended to increase in a dose-dependent manner.[20] Postprocedural MI was defined as postprocedural creatine phosphokinase values greater than three times the upper limit. Cardiogenic shock was defined as a sustained (>30min) episode of systolic blood pressure <90mmHg, a cardiac index of $<2.2\,L\cdot min^{-1}\cdot m^{-2}$ determined to be secondary to cardiac dysfunction, and/or the requirement for parenteral inotropic or vasopressor agents

Table 4. Baseline Clinical Characteristics of STEMI Patients in Each Group According to Use of Preprocedural Antiplatelet Therapy

	Non-DAPT (n=650), % (n)	DAPT (n=1,274), % (n)	P value
Age, years (median)	66.8±12.4	65.1±12.4	0.006
50–59	20.8 (135)	22.6 (288)	0.358
60–69	31.4 (204)	33.2 (423)	0.421
70–79	28.2 (183)	26.3 (335)	0.385
>80	15.5 (101)	13.3 (169)	0.175
Female	22.6 (147)	19.8 (252)	0.147
BMI	24.1±3.7	23.6±3.7	0.972
Coronary risk factors			
DM	32.0 (208)	31.6 (403)	0.870
DM with insulin	3.7 (24)	4.4 (56)	0.465
Hypertension	62.3 (405)	61.8 (787)	0.820
Hyperlipidemia	51.8 (337)	57.1 (727)	0.029
Smoking	45.7 (297)	45.4 (578)	0.893
Comorbidities			
CVD	6.6 (43)	7.2 (92)	0.623
COPD	2.9 (19)	1.9 (24)	0.145
CKD stage ≥3	10.8 (70)	10.1 (129)	0.661
PAD	2.8 (18)	3.4 (43)	0.473
History			
Prior MI	3.2 (21)	3.2 (41)	0.988
Prior HF	3.8 (25)	2.1 (27)	0.027
Prior CABG	1.2 (8)	0.9 (11)	0.441
Presenting status			
HF	17.1 (111)	11.1 (141)	<0.001
NYHA class 3/4	10.3 (67)	7.1 (91)	0.017
Coronary status			
2-vessel disease	33.7 (219)	38.5 (490)	0.040
3-vessel disease	20.3 (132)	22.6 (288)	0.248
LMT stenosis	5.1 (33)	6.0 (77)	0.388
PCI indication			
STEMI <12h	73.8 (480)	70.4 (897)	0.114
STEMI >12h, unstable	18.2 (118)	18.1 (230)	0.957
Puncture site			
Radial artery	7.1 (46)	21.6 (275)	<0.001
Femoral artery	91.5 (595)	77.7 (990)	<0.001
Door to balloon time (min)	104.9±62.8	98.0±57.6	0.044

Abbreviations as in Table 1.

or mechanical support. Heart failure (HF) was defined as physician documentation or report of any of the following clinical symptoms of HF: unusual dyspnea or rales on light exertion, jugular venous distension, pulmonary edema on physical examination, or pulmonary edema evident on a chest radiograph presumably associated with cardiac dysfunction.

Information Disclosure

Before the launch of the JCD, information on the objectives of the present study, its social significance, and an abstract were provided to register this clinical trial with the University Hospital Medical Information Network. This Network is recognized by the International Committee of Medical Journal Editors as an acceptable registry, according to a statement issued in September 2004 (UMIN R000004736).

Participants

Major teaching hospitals within the metropolitan Tokyo area were selected for this study, and the study protocol was approved by the institutional review board committee at each site. Informed consent was waived because this was a database-oriented study. All consecutive PCI patients older than 18 years during the study period were registered, including failure cases.

Procedures and Data Collection

We analyzed data from 6,528 patients who had undergone PCI at any 1 of the 12 Japanese hospitals participating in the JCD between September 2008 and September 2013. Acute coronary syndrome (ACS) was defined as the patient presenting to the hospital with STEMI or NSTEMI/unstable angina (NSTE-ACS). We excluded patients who presented with preprocedural cardiopulmonary arrest or with preprocedural cardiogenic shock. Patients included in this study were divided into 2 groups based on preprocedural antiplatelet therapy: DAPT users and non-users.

Table 5. Outcomes of STEMI Patients in Each Group According to Use of Preprocedural Antiplatelet Therapy

	Non-DAPT (n=656), % (n)	DAPT (n=1,265), % (n)	P value
Death, shock, HF	10.9 (71)	6.9 (88)	0.002
Death	2.8 (18)	2.6 (33)	0.817
Shock	3.8 (25)	3.2 (41)	0.474
HF	7.1 (46)	3.5 (44)	<0.001
Coronary dissection	1.8 (12)	1.0 (13)	0.130
Coronary perforation	1.1 (7)	0.8 (10)	0.517
Cerebral infarction	0.9 (6)	0.6 (7)	0.344
Cerebral bleeding	0.2 (1)	0.1 (1)	0.628
Cardiac tamponade	0.8 (5)	0.7 (9)	0.878
HD introduction	2.0 (13)	0.3 (4)	<0.001
Thrombosis	0.0 (0)	0.2 (3)	0.216
Blood transfusion	2.5 (16)	2.2 (28)	0.714
Bleeding <72h			
Puncture site	0.6 (4)	0.9 (11)	0.558
Hematoma	0.8 (5)	0.7 (9)	0.878
Retroperitoneal hemorrhage	0.2 (1)	0.0 (0)	0.161
Gastrointestinal bleeding	0.8 (5)	0.4 (5)	0.277
Urological bleeding	0.2 (1)	0.2 (3)	0.710
Other bleeding	1.2 (8)	1.3 (16)	0.963
Postprocedural MI	80.5 (503)	75.3 (940)	0.012

Abbreviations as in Tables 1,3.

Statistical Analysis and Study Endpoints

The study endpoints included in-hospital mortality, cardiogenic shock, HF, postprocedural MI (postprocedural creatine phosphokinase more than three times the upper limit), and bleeding complications. Bleeding complications in this registry were defined as those requiring transfusion, prolonging the hospital stay, and/or causing a decrease in hemoglobin level of >3.0 g/dl.

Continuous variables are expressed in terms of their means and standard deviations. Categorical variables are expressed as percentages. Continuous variables were compared by Student's t-test, and differences between categorical variables were examined by χ^2 test. A multiple logistic regression analysis was performed to determine the independent predictors for in-hospital mortality, cardiogenic shock, HF, bleeding, and postprocedural MI. We performed covariate adjustment by using the propensity score; using this approach, the aforementioned outcome variables were regressed on an indicator variable denoting DAPT treatment status and the estimated propensity score. Factors included in the statistical model were the use/non-use of DAPT, age, female sex, previous MI, previous HF, diabetes mellitus, cerebrovascular disease, arteriosclerosis obliterans, chronic obstructive pulmonary disease, hypertension, smoking, juvenile coronary artery disease, history of coronary artery bypass grafting (CABG), chronic kidney disease stage ≥3, body mass index ≥30 kg/m^2, and propensity score for use of DAPT.

All statistical calculations and analyses were performed using SPSS version 20 (SPSS, Chicago, IL, USA), and P-values <0.05 were considered statistically significant.

Ethical Considerations

The JCD Steering Committee was responsible for overall study guidance, including the study protocol, data analyses, and interpretation of results. The Department of Healthcare Quality Assessment at Tokyo University independently managed the database. During the planning, implementation, and reporting of this study, there were no issues such as conflicts of interest, conflicts of responsibility, or intellectual property right concerns.

Results

A total of 6,528 consecutive patients who had undergone PCI during the study period were assessed. The average age of the patients was 67.4±11.4 years, and 1,366 patients (20.9%) were women. The number of patients with STEMI, NSTE-ACS, and stable angina was 1,924 (29.5%), 1,921 (29.4%), and 1,452 (22.2%), respectively. Of the 6,528 patients, 2,079 (31.8%) did not receive preprocedural DAPT. The majority of these non-DAPT patients received aspirin (89.6%), but the dispensing rates of second antiplatelet agents such as clopidogrel, ticlopidine, and cilostazol were low, with 59 (2.8%), 70 (3.4%), and 45 (2.2%) patients, respectively, receiving these agents.

Patient Population

The baseline clinical characteristics of the DAPT and non-DAPT groups are presented in **Table 1**. The numbers of patients who presented with hyperlipidemia, chronic kidney disease stage ≥3, prior HF, NSTEMI/unstable angina, and stable angina as indicators of PCI and radial artery puncture were significantly higher in the DAPT group than in the non-DAPT group. Prior HF, Canadian Cardiovascular Society (CCS) class 3/4 angina, STEMI as a PCI indicator, and femoral artery puncture were more common in the non-DAPT group.

Propensity Score Analysis (Variables Associated With Non-Use of DAPT)

Table 2 shows the variables associated with non-use of pre-

Table 6. Baseline Clinical Characteristics of NSTE-ACS Patients in Each Group According to Use of Preprocedural Antiplatelet Therapy

	Non-DAPT (n=656), % (n)	DAPT (n=1,265), % (n)	P value
Age, years (median)	68.8±11.5	67.9±11.5	0.127
50–59	13.4 (88)	18.2 (230)	0.008
60–69	26.2 (172)	31.5 (399)	0.016
70–79	24.8 (163)	34.8 (440)	<0.001
>80	15.4 (101)	15.9 (201)	0.778
Female	26.2 (172)	21.5 (272)	0.020
BMI	23.9±3.6	24.2±3.7	0.088
Coronary risk factors			
DM	31.6 (207)	33.0 (417)	0.532
DM with insulin	5.2 (34)	5.0 (63)	0.847
Hypertension	67.5 (443)	66.5 (841)	0.644
Hyperlipidemia	55.6 (365)	58.7 (743)	0.193
Smoking	34.6 (277)	35.8 (453)	0.600
Comorbidities			
CVD	10.7 (70)	7.4 (93)	0.013
COPD	3.7 (24)	2.5 (31)	0.132
CKD stage ≥3	9.0 (59)	14.3 (181)	0.001
PAD	5.3 (25)	4.3 (54)	0.292
History			
Prior MI	5.5 (36)	5.1 (64)	0.688
Prior HF	5.8 (38)	5.4 (68)	0.704
Prior CABG	4.3 (28)	2.3 (29)	0.016
Presenting status			
CCS class 3/4	51.5 (338)	52.5 (664)	0.688
CCS class 4	30.5 (200)	25.6 (324)	0.023
HF	14.0 (92)	14.4 (182)	0.829
NYHA class 3/4	9.0 (59)	10.0 (126)	0.496
Coronary status			
2-vessel disease	34.8 (228)	45.6 (577)	<0.001
3-vessel disease	18.1 (119)	23.8 (301)	0.004
LMT stenosis	7.5 (49)	9.0 (114)	0.250
PCI indication			
NSTEMI	30.3 (199)	33.8 (427)	0.129
UA	69.7 (457)	66.2 (838)	0.129
Puncture site			
Radial artery	24.2 (159)	39.4 (499)	<0.001
Femoral artery	73.0 (479)	58.8 (740)	<0.001

ACS, acute coronary syndrome. Other abbreviations as in Table 1.

procedural DAPT after adjustment: female sex (odds ratio [OR]: 0.84, 95% confidence interval [CI]: 0.73–0.97, P<0.001), prior CABG (OR: 0.57, 95% CI: 0.43–0.77, P<0.001), CCS class 4 (OR: 0.71, 95% CI: 0.59–0.85, P<0.001), and HF on admission (OR: 0.60, 95% CI: 0.50–0.71, P<0.001) were all associated with DAPT non-use.

In-Hospital Crude Outcomes

Table 3 shows the overall in-hospital outcomes and complications for the 2 groups. The combined rate of death, postprocedural shock, and HF was significantly higher in the non-DAPT group than in the DAPT group. Rates of hemodialysis introduction and postprocedural MI were also higher in the non-DAPT group than in the DAPT group. Notably, the rates of stent thrombosis and bleeding complications were similar in both groups.

In-Hospital Adjusted Outcomes

Multivariate logistic regression analysis showed that DAPT use was 1 of the independent predictors for improved combined outcomes of death, postprocedural shock, and HF (OR: 0.68, 95% CI: 0.51–0.91, P=0.009), and for postprocedural MI (OR: 0.71, 95% CI: 0.59–0.85, P<0.001). Receiving preprocedural DAPT showed noninferiority in bleeding complications (OR: 1.02, 95% CI: 0.63–1.40, P=0.764) (**Figure A**).

Subgroup analyses of STEMI and NSTE-ACS were performed (**Tables 4–7**). In the STEMI subgroup, DAPT use was associated with reduced risk of postprocedural MI (OR: 0.74, 95% CI: 0.57–0.96, P=0.026). There was also a trend toward a lower risk for combined outcomes of death, postprocedural shock, and HF (OR: 0.73, 95% CI: 0.51–1.04, P=0.079). In the NSTE-ACS subgroup, DAPT use was associated with reduced risk of postprocedural MI (OR: 0.69, 95% CI: 0.52–0.92, P=0.012). No additional risk of bleeding complications was

Table 7. Outcomes of NSTE-ACS Patients in Each Group According to Use of Preprocedural Antiplatelet Therapy

	Non-DAPT (n=656), % (n)	DAPT (n=1,265), % (n)	P value
Death, shock, HF	3.5 (23)	2.5 (32)	0.224
Death	1.4 (9)	0.8 (10)	0.222
Shock	2.3 (15)	0.9 (12)	0.018
HF	1.7 (11)	1.1 (14)	0.296
Coronary dissection	0.9 (6)	0.9 (12)	0.942
Coronary perforation	0.6 (4)	0.7 (9)	0.797
Cerebral infarction	0.9 (6)	0.6 (7)	0.360
Cerebral bleeding	0.0 (0)	0.0 (0)	
Cardiac tamponade	0.2 (1)	0.2 (2)	0.976
HD introduction	2.0 (13)	0.9 (12)	0.058
Thrombosis	0.0 (0)	0.2 (3)	0.212
Blood transfusion	2.7 (18)	1.4 (18)	0.043
Bleeding <72h			
Puncture site	0.6 (4)	0.9 (11)	0.540
Hematoma	0.9 (6)	1.1 (14)	0.694
Retroperitoneal hemorrhage	0.0 (0)	0.1 (1)	0.471
Gastrointestinal bleeding	0.6 (4)	0.3 (4)	0.343
Urological bleeding	0.2 (1)	0.2 (2)	0.976
Other bleeding	1.1 (7)	0.6 (8)	0.305
Postprocedural MI	18.6 (98)	15.2 (178)	0.083

Abbreviations as in Tables 1,3,6.

noted in either the STEMI (OR: 0.89, 95% CI: 0.49–1.63, P=0.710) or the NSTE-ACS (OR: 1.02, 95% CI: 0.51–2.03, P=0.952) subgroup (**Figures B,C**).

Discussion

Approximately one-third of Japanese patients do not receive preprocedural DAPT before undergoing PCI despite the strong recommendations from clinical guidelines. The rate of preprocedural DAPT use in the present study was consistent with previously reported registry data,[13] suggesting that our data were representative of a real-world situation. In our propensity-adjusted analysis of the multicenter registry data, DAPT use before undergoing PCI was associated with reduced risk of postprocedural MI. DAPT use showed a clinically noticeable, although not significant, trend toward reduced risk of combined outcomes of death, postprocedural cardiogenic shock, and HF. This was consistent across all subgroups, including patients with STEMI and NSTE-ACS.

Although DAPT is frequently used to reduce acute thrombotic events in modern PCI management, its efficacy in Japanese patients, who are susceptible to bleeding complications, remains controversial. Previous studies of patients with ACS, particularly those who have undergone PCI, have shown that preprocedural DAPT has beneficial effects, possibly by reducing subacute stent thrombosis, periprocedural ischemia, and distal embolization. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial,[3] early administration of clopidogrel decreased the number of Q-wave MI and significantly improved in-hospital and 1-year outcomes. The Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARMYDA-2) study[21] showed that 600 mg clopidogrel administered preprocedurally significantly reduced periprocedural MI compared with 300 mg clopidogrel, possibly by greater and faster platelet inhibition. After publication of those studies and inclusion as well as implementation in the guidelines, pretreatment with 300 mg clopidogrel before PCI has been widely used in PCI management in Japan. The present study confirmed that DAPT non-users have a greater degree of postprocedural myocardial damage. The effect of periprocedural MI on the long-term prognosis for patients undergoing PCI has been controversial;[22–26] however, the occurrence of periprocedural MI above a certain threshold seems to be associated with a higher risk of late mortality.

Because previous studies have shown a significant association between guideline-based care processes and in-hospital mortality,[27] further efforts to implement the appropriate clinical use of DAPT are necessary. Nevertheless, issues do arise that lead to omission of DAPT, such as the patient's inability to take oral medication, true contraindications such as allergy and active bleeding, or the primary medical staff not recognizing the importance of preprocedural DAPT. These omissions may have different clinical impacts. In addition, our study indicated that prior CABG, CCS class 4, and HF on admission were independent predictors of preprocedural DAPT non-use. Patients with significant angina, such as those with CCS class 4, may be rushed to the catheter laboratory with inadequate time for DAPT administration, and it may be difficult for patients with HF to take oral medication. Recognizing these clinical scenarios as potential causes of DAPT non-use could aid in improving the implementation of appropriate care and patient outcomes by developing solutions for such situations. Our data also showed differences in the rate of DAPT use among hospitals (**Figure S1**).

The incidence of procedure-related bleeding associated with DAPT use has varied in previous studies. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial[28] for primary prevention and the CURE trial[3] for secondary prevention of NSTE-ACS showed an increased risk of long-term bleeding in DAPT users. In contrast, PCI-related trials, such as PCI-CURE,[29] PCI-Clopidogrel as Adjunctive Reperfusion Therapy

(CLARITY),[2] Clopidogrel for the Reduction of Events During Observation (CREDO),[1] and ARMYDA-2,[21] showed that DAPT did not increase the risk of short-term bleeding complications. Our study results agreed with these findings. We also noted that the incidence of bleeding events was similar to that of the J-AMI registry[13] This is of particular importance, because East Asians, including Japanese, are known to be vulnerable to bleeding during invasive procedures. Previous studies have shown that Asian patients with NSTE-ACS have a significantly higher bleeding risk than non-Asian Caucasians (13.4% vs. 9.4%, P<0.0001),[11] indicating ethnic variability in antithrombotic susceptibility.[30] A lower loading dose of clopidogrel (300 mg) and/or frequent use of radial artery access might have contributed to lowering the risk of bleeding in our dataset.

Study Limitations

First, because this study was an analysis of a multicenter cohort study rather than an observational and nonrandomized trial, unmeasured and unaccounted variables may have confounded the observed associations. Second, the study population was limited. Despite a large number of procedures performed in Japan (>200,000 annually), the number of procedures performed in each hospital was limited. Third, specific reasons for DAPT non-use were not available in the JCD Keio interhospital Cardiology Study database. The condition of patients in the non-DAPT group may have been more critical than that of patients in the DAPT group, which could have biased the results. For example, intravascular ultrasound imaging was used more frequently in the non-DAPT group (40.2% vs. 20.2%; P<0.001, respectively for non-DAPT and DAPT groups). Because the overall procedure-related complications were similar (2.2% vs. 2.1%; P=0.49), the inadequate use of intravascular imaging is probably not the sole reason for increased events, but does represent the complexity of this issue. Fourth, warfarin intake data were not available in the database, and could affect both the decision to forgo DAPT and the bleeding rate. The use of warfarin at discharge was noted to be higher in the non-DAPT compared with the DAPT group (7.7% vs. 9.9%; P<0.001), albeit a relatively low rate of warfarin use in both groups likely precludes a major effect of anticoagulation therapy in our analysis. Fifth, neither genetic phenotype information nor the quantitative information of thienopyridine resistance was available in our dataset. However, according to our present data (and also consistent with the result from J-AMI registry), the rate of stent thrombosis was substantially lower than that of non-Asians. Sixth, the exact timing of DAPT administration before PCI was unavailable in the database. Finally, we did not evaluate the effect of preprocedural DPAT on long-term clinical outcomes among patients who had undergone PCI. This should be a future consideration.

Conclusions

A significant number of Japanese PCI patients do not receive preprocedural DAPT; however, in our study, PCI patients who underwent DAPT had a lower combined risk of death, postprocedural shock, HF, and a lower risk of postprocedural MI without any obvious risk of bleeding. Thus, preprocedural DAPT seems to be beneficial across patient populations, and further effort is needed to implement the use of DAPT in real-world PCI.

Acknowledgments

This research was supported by a grant from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (KAKENHI No. 25460630 [S.K.] and 25460777 [I.U.]) and by Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science.

Conflicts of Interest

None.

Contributors

Y.I., S.K., and I.U. conceived and designed the research, and drafted the manuscript. Y.I., S.K., and H.M. analyzed and interpreted the data. H.M. performed the statistical analysis. S.K. and K.F. handled funding and supervision; J.F., M.S., Y.S., Y.N., K.N., I.N., Y. Maekawa, Y. Momiyama, K.F. made critical revisions of the manuscript for important intellectual content.

References

1. Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: A randomized controlled trial. *JAMA* 2002; **288:** 2411–2420.
2. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: The PCI-CLARITY study. *JAMA* 2005; **294:** 1224–1232.
3. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; **345:** 494–502.
4. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **61:** e78–e140, doi:10.1016/j.jacc.2012.11.019.
5. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation* 2011; **124:** e574–e651, doi:10.1161/CIR.0b013e31823ba622.
6. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *EuroIntervention* 2015; **10:** 1024–1094.
7. Japanese Circulation Society guidelines for the management of patients with ST-elevation myocardial infarction 2008 [in Japanese].
8. Japanese Circulation Society guidelins for the management of patients without persistent ST segment elevation 2007 [in Japanese].
9. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, et al. 2014 AHA/ACC Guideline for the management of patients with non-ST-elevation acute coronary syndromes. *Journal of the American College of Cardiology* 2014; **64:** e139–e228, doi:10.1016/j.jacc.2014.09.017.
10. JCS Joint Working Group. Guidelines for elective percutaneous coronary intervention in patients with stable coronary artery disease (JCS 2011) published in 2012: Digest version. *Circ J* 2013; **77:** 1590–1607.
11. Wang TY, Chen AY, Roe MT, Alexander KP, Newby LK, Smith SC Jr, et al. Comparison of baseline characteristics, treatment patterns, and in-hospital outcomes of Asian versus non-Asian white Americans with non-ST-segment elevation acute coronary syndromes from the CRUSADE quality improvement initiative. *Am J Cardiol* 2007; **100:** 391–396.
12. Kawaji T, Shiomi H, Morimoto T, Tamura T, Nishikawa R, Yano M, et al. Long-term efficacy and safety outcomes after unrestricted use of drug-eluting stents in patients with acute coronary syndrome. *Circ J* 2014; **78:** 1628–1635.
13. Nakamura M, Yamagishi M, Ueno T, Hara K, Ishiwata S, Itoh T, et al. Current Antiplatelet therapy for Japanese patients with ST elevation acute myocardial infarction: J-AMI registry. *Cardiovasc Interv Ther* 2013; **28:** 162–169.
14. Mogi S, Kohsaka S, Miyata H, Kawamura A, Noma S, Suzuki M, et

al. Comparison between working day and holiday acute coronary syndrome presentation. *Int J Cardiol* 2011; **153:** 85–87.
15. Ohno Y, Maekawa Y, Miyata H, Inoue S, Ishikawa S, Sueyoshi K, et al. Impact of periprocedural bleeding on incidence of contrast-induced acute kidney injury in patients treated with percutaneous coronary intervention. *J Am Coll Cardiol* 2013; **62:** 1260–1266.
16. Kodaira M, Kawamura A, Miyata H, Noma S, Suzuki M, Ishikawa S, et al. Door to balloon time: How short is enough under highly accessible nationwide insurance coverage? Analysis from the Japanese multicenter registry. *Int J Cardiol* 2013; **168:** 534–536.
17. Numasawa Y, Kohsaka S, Miyata H, Kawamura A, Noma S, Suzuki M, et al. Safety of transradial approach for percutaneous coronary intervention in relation to body mass index: A report from a Japanese multicenter registry. *Cardiovasc Interv Ther* 2013; **28:** 148–156.
18. Messenger JC, Ho KK, Young CH, Slattery LE, Draoui JC, Curtis JP, et al. The National Cardiovascular Data Registry (NCDR) data quality brief: The NCDR data quality program in 2012. *J Am Coll Cardiol* 2012; **60:** 1484–1488.
19. Ogawa H, Hokimoto S, Kaikita K, Yamamoto K, Chitose T, Ono T, et al. Current status and prospects of antiplatelet therapy in percutaneous coronary intervention in Japan: Focus on adenosine diphosphate receptor inhibitors. *J Cardiol* 2011; **58:** 6–17.
20. Nakagawa Y, Nobuyoshi M, Yamaguchi T, Meguro T, Yokoi H, Kimura T, et al. Efficacy of abciximab for patients undergoing balloon angioplasty: Data from Japanese evaluation of c7E3 Fab for elective and primary PCI organization in randomized trial (JEPPORT). *Circ J* 2009; **73:** 145–151.
21. Patti G, Colonna G, Pasceri V, Pepe LL, Montinaro A, Di Sciascio G. Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention: Results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) study. *Circulation* 2005; **111:** 2099–2106.
22. Prasad A, Gersh BJ, Bertrand ME, Lincoff AM, Moses JW, Ohman EM, et al. Prognostic significance of periprocedural versus spontaneously occurring myocardial infarction after percutaneous coronary intervention in patients with acute coronary syndromes: An analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. *J Am Coll Cardiol* 2009; **54:** 477–486.
23. Damman P, Wallentin L, Fox KA, Windhausen F, Hirsch A, Clayton T, et al. Long-term cardiovascular mortality after procedure-related or spontaneous myocardial infarction in patients with non-ST-segment elevation acute coronary syndrome: A collaborative analysis of individual patient data from the FRISC II, ICTUS, and RITA-3 trials (FIR). *Circulation* 2012; **125:** 568–576.
24. Jang JS, Jin HY, Seo JS, Yang TH, Kim DK, Kim DS, et al. Prognostic value of creatine kinase-myocardial band isoenzyme elevation following percutaneous coronary intervention: A meta-analysis. *Catheter Cardiovasc Interv* 2013; **81:** 959–967.
25. Zimarino M, Affinito V. The prognosis of periprocedural myocardial infarction after percutaneous coronary interventions. *Cardiovasc Revasc Med* 2013; **14:** 32–36.
26. Gili S, D'Ascenzo F, Moretti C, Omede P, Vilardi I, Bertaina M, et al. Impact on prognosis of periprocedural myocardial infarction after percutaneous coronary intervention. *J Interv Cardiol* 2014; **27:** 482–490.
27. Peterson ED, Roe MT, Mulgund J, DeLong ER, Lytle BL, Brindis RG, et al. Association between hospital process performance and outcomes among patients with acute coronary syndromes. *JAMA* 2006; **295:** 1912–1920.
28. Bhatt DL, Topol EJ. Clopidogrel added to aspirin versus aspirin alone in secondary prevention and high-risk primary prevention: Rationale and design of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. *Am Heart J* 2004; **148:** 263–268.
29. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: The PCI-CURE study. *Lancet* 2001; **358:** 527–533.
30. Nakata T, Miyahara M, Nakatani K, Wada H, Tanigawa T, Komada F, et al. Relationship between CYP2C19 loss-of-function polymorphism and platelet reactivities with clopidogrel treatment in Japanese patients undergoing coronary stent implantation. *Circ J* 2013; **77:** 1436–1444.

Supplementary Files

Supplementary File 1

Figure S1. Use of dual antiplatelet therapy (DAPT) in each institute participating in study of use of preprocedural antiplatelet therapy in Japanese patients undergoing percutaneous coronary intervention.

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-15-0484

An international comparison of patients undergoing percutaneous coronary intervention: A collaborative study of the National Cardiovascular Data Registry (NCDR) and Japan Cardiovascular Database–Keio interhospital Cardiovascular Studies (JCD-KiCS)

Shun Kohsaka, MD, PhD,[a] Hiroaki Miyata, PhD,[b] Ikuko Ueda, PhD,[a] Frederick A. Masoudi, MD, MSPH,[c,d] Eric D. Peterson, MD, MPH,[e] Yuichiro Maekawa, MD,[a] Akio Kawamura, MD,[a] Keiichi Fukuda, MD, PhD,[a] Matthew T. Roe, MD, MHS,[e] and John S. Rumsfeld, MD, PhD[c,d], on behalf of the JCD-KiCS and NCDR *Tokyo, Japan; Aurora, Denver, CO; and Durham, NC*

Background Details on Japanese patients undergoing percutaneous coronary intervention (PCI) and how they compare to US patients remain unclear. Furthermore, the application of US risk models has not been evaluated internationally.

Methods The JCD-KiCS, a multicenter registry of consecutive PCI patients, was launched in 2008, with variables defined in accordance with the US NCDR. Patient and procedural characteristics from patients enrolled from 2008 to 2010 in the JCD-KiCS database (n = 9,941) and those in the NCDR (n = 732,345) were compared. The primary outcomes of this analysis were the hospital-level all-cause mortality and bleeding complications. The NCDR risk models for these 2 outcomes were evaluated in the Japanese data set; from the expected mortality and bleeding rates, the observed/expected ratios were calculated.

Results The Japanese patients were older, with a higher proportion of men, diabetes, and smoking than the US patients. The Japanese patients also had a higher rate of complex lesions (26.1 vs 12.7% for bifurcation and 6.2% vs 3.2% for chronic total occlusions, all $P < .001$), longer procedure time (29.7 ± 21.5 vs 14.4 ± 11.5 minutes, $P < .001$), and higher mortality (1.6% vs 0.9%, $P < .001$) and bleeding rates (2.9% vs 1.8%, $P < .001$) compared with US patients. The observed/expected ratios for mortality and bleeding were 0.921 and 0.467, respectively, in Japanese patients, and 1.002 and 0.981, respectively, for US patients.

Conclusions The characteristics of patients undergoing PCI in clinical practice in Japan and the US differ substantially. The NCDR risk models applied well in Japanese patients for prediction of mortality, but not for bleeding, which tended to underestimate the risk. (Am Heart J 2015;170:1077-85.)

Clinical registry programs are increasingly used to measure the patient characteristics, care delivery, and outcomes of patients in clinical practice within multiple countries, including Japan and the United States.[1] However, to date, only a few direct comparisons among international registry programs have been made, limiting the abilities to evaluate the contemporary cardiovascular practice and outcomes globally. This is, at least in part, due to a lack of common data elements for comparison, which in turn limits valid direct comparisons of patient characteristics, procedure results, and outcomes.

The NCDR CathPCI Registry, which was initiated in 1998, is the largest US national clinical registry program for percutaneous coronary intervention (PCI). The captured data are based on standardized data elements and definitions, including detailed patient characteristics, procedural findings, and outcomes. In Japan, the JCD-KiCS, established in 2008, is another large, multicenter registry designed to collect data on consecutive PCI patients. The JCD-KiCS registry has adopted the NCDR data elements/definitions to enable a direct comparison

From the [a]Keio University, Tokyo, Japan, [b]Tokyo University, Tokyo, Japan, [c]University of Colorado, Aurora, CO, [d]The Denver Veterans Affairs Medical Center, Denver, CO, and [e]Duke University, Durham, NC.

The present study was funded by the Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (25460630 and 25460777) and the National Cardiovascular Data Registry. The authors disclose no relationship with the industry. Dr Masoudi is a Senior Medical Officer, and Dr. Rumsfeld is the Chief Science Officer for the NCDR.

Submitted November 24, 2014; accepted September 10, 2015.

Reprint requests: Shun Kohsaka, MD, PhD, Division of Cardiology, School of Medicine, Keio University, 35 Shinanomachi, Tokyo, Japan.

E-mail: kohsaka@cpnet.med.keio.ac.jp

0002-8703

http://dx.doi.org/10.1016/j.ahj.2015.09.017

of the care and outcomes. The aims of this study were to (a) compare the patient characteristics and procedural indications, (b) compare the coronary anatomy and procedure details, and (c) compare the periprocedural outcomes between the Japanese and US clinical registry cohorts, including the applications of the NCDR mortality and bleeding complication risk models. To our knowledge, this is one of the first international comparisons of PCI practice using clinical registry data and may reflect on the importance of common data standards and risk adjustments for international quality of care comparisons.

Methods

Study design

The NCDR CathPCI Registry is co-sponsored by the American College of Cardiology and the Society for Cardiovascular Angiography and Intervention. There are currently more than 1500 participating centers across the United States. Quality assurance of the data is achieved through automatic system validation and reporting of data completeness, education and training for site data managers, and random on-site auditing.[2] Only institutions whose data submissions meet the NCDR quality criteria for reporting are included.

The JCD-KiCS is a prospective multicenter registry designed to collect clinical variables and outcome data on consecutive PCI patients, with dedicated clinical research coordinators assigned to each site. The clinical variables and in-hospital outcomes for the JCD were defined in accordance with those specified for CathPCI Registry v4.1 (NCDR) in order to enable a direct comparison with the NCDR CathPCI Registry program.

In the present analysis, JCD-KiCS data (9,941 patients; 16 hospitals in Kanto, Japan [Tokyo, Tochigi, Saitama, Chiba, and Kanagawa Prefecture]; September 2008–December 2010) were compared with the NCDR CathPCI Registry data (732,345 patients; 1166 sites; April 2008–September 2010). Informed consent was routinely obtained from patients before undergoing PCI. The participating hospitals were mostly large tertiary care referral centers (>200 beds; n = 12), but included a few midsized satellite hospitals (<200 beds; n = 4). The average annual case-volume was 331 (ranging from 104 to 517) during the study period. The hospitals were instructed to record and register data from consecutive hospital visits for PCI using an Internet-based database system. Percutaneous coronary intervention with any commercially available coronary device was included. The data entered were checked for completeness and internal consistency. Quality assurance of the data was achieved through automatic system validation and reporting of data completeness, and through education and training for the dedicated clinical research coordinators specifically trained for the present PCI registry. The senior study coordinator (I.U.), along with exclusive on-site auditing by the investigators (S.K., A.K., and H.M.), ensured proper registration of each patient.

Information disclosure

The study protocol was approved by the institutional review board committee at each site in Japan; the NCDR data use was approved by Chesapeake and Duke Universities' institutional review boards. Before the launch of the JCD, information on the objectives of the present study, its social significance, and an abstract were provided for clinical trial registration with the University Hospital Medical Information Network, which is recognized by the International Committee of Medical Journal Editors as an "acceptable registry" according to a statement issued in September 2004 (UMIN R000004736).

The JCD Steering Committee was responsible for the overall study guidance, including the study protocol, data analysis, and interpretation of the results. The study analyses for the NCDR data set was supported by Ms Sarah Milford-Beland (MS). The Department of Healthcare Quality Assessment at Tokyo University independently managed the JCD database. The Keio Interhospital Cardiology Study (KiCS) Group managed the participating sites and provided a monthly on-site monitoring service to assure data accuracy and completeness throughout the study.

All patients who underwent PCI at the JCD-KiCS participating sites were included. Following the standard NCDR data definitions used in both registry programs, bleeding was defined as (1) occurring at the percutaneous entry site, during or after the catheterization laboratory visit until discharge, which may be external or a hematoma >10 cm for femoral, >5 cm for brachial, or >2 cm for radial access; (2) retroperitoneal; (3) gastrointestinal; (4) genitourinary; and (5) bleeding of other/unknown origin during or after the catheterization laboratory visit until discharge. All bleeding events required a transfusion and/or were associated with a drop in hemoglobin >3.0 g/dL. These bleeding criteria are consistent with the Bleeding Academic Research Consortium grades 3A-C.[3] Additional data elements and definitions can be found at www.ncdr.com. Of note, low-molecular-weight heparin, glycoprotein IIb/IIIa receptor antagonists, and bivalirudin were not available for use during the study period in Japan.

Statistical analysis

The primary outcomes of this comparative analysis were the hospital-level all-cause mortality and bleeding complications. Descriptive statistics were calculated based on the clinical characteristics and treatment information of the registered patients. The comparative analysis was performed in Tokyo University, Department of Health Quality Assessment (H.M.). Variables were compared using bivariate tests, including the χ^2 test for

Table I. Baseline patient characteristics according to the indications for PCI in the US and Japan

	United States				Japan			
	Overall (n = 732,345)	Elective (stable/No Angina; n = 232,111)	UA/NSTEMI (n = 394,612)	STEMI (n = 105,622)	Overall (n = 9941)	Elective (stable/no angina; n = 5030)	UA/NSTEMI (n = 2631)	STEMI (n = 2288)
Mean age (y)	64.6 ± 12.1	66.2 ± 11.1	64.7 ± 12.2	61.1 ± 13.0	67.9 ± 10.8	68.2 ± 9.8	68.7 ± 11.1	66.5 ± 12.4
Age ≥80 y (%)	12.2	12.1	12.8	10.3	14.0	11.6	17.1	15.9
Sex (male; %)	67.2	68.5	65.3	71.5	79.2	81.0	76.6	78.2
BMI (kg/m^2)	30.0 ± 6.4	30.2 ± 6.4	30.1 ± 6.5	29.1 ± 6.1	24.2 ± 3.6	24.4 ± 3.5	24.0 ± 3.6	23.8 ± 3.7
BMI ≥30 kg/m^2 (%)	43.3	44.5	44.2	37.2	6.1	6.7	5.7	5.2
Previous MI (%)	29.6	30.4	32.0	19.4	25.4	34.4	21.8	10.0
Previous heart failure (%)	11.3	12.3	12.5	4.6	8.8	11.1	8.7	4.0
Diabetes (%)	35.7	38.1	37.5	24.1	42.7	47.5	40.7	34.6
Insulin diabetes (%)	12.8	13.2	14.1	6.7	8.8	10.7	8.3	5.1
Cerebrovascular disease (%)	12.1	12.6	13.1	7.0	8.1	9.4	9.7	7.6
Peripheral vascular disease (%)	12.4	14.2	13.0	6.1	7.2	10.7	7.0	3.7
Chronic lung disease (%)	14.9	14.5	16.4	10.3	3.1	3.2	3.5	2.4
Hypertension (%)	81.8	85.6	83.8	66.0	74.2	77.9	75.1	65.2
Current/recent smoker (%)	27.5	20.8	27.3	42.8	34.7	30.0	34.7	45.2
Dyslipidemia (%)	80.3	85.1	82.1	63.2	66.6	71.3	65.1	57.8
Family history CAD (age <55 y; %)	24.7	25.0	25.5	21.1	15.2	15.1	14.9	15.8
Previous PCI (%)	40.3	45.2	42.6	20.9	36.9	52.4	31.4	9.0
Previous CABG (%)	18.9	20.1	21.7	6.0	5.4	6.9	5.9	1.7
Dialysis (%)	2.3	2.5	2.5	1.0	4.4	5.0	5.8	1.2
Mean GFR	75.2 ± 30.3	74.2 ± 29.5	75.5 ± 30.6	76.3 ± 30.5	86.6 ± 34.2	85.2 ± 32.0	84.2 ± 36.3	92.4 ± 35.2
Noninvasive yesting								
All tests (%)	35.0	58.4	29.7	3.1	36.5	60.0	21.5	2.2
Double master testing (%)*	–	–	–	–	5.0	7.3	4.5	0.6
Exercise treadmill testing (%)	3.4	5.7	2.8	0.3	8.8	14.6	4.9	0.4
Exercise echo testing (%)*	3.5	5.7	3.1	0.3	–	–	–	–
Nuclear imaging study (%)	26.7	45.7	22.4	1.2	16.5	28.1	8.0	0.7
Coronary CT angiogram (%)	1.0	1.8	0.8	0.04	18.2	31.5	7.6	1.0

Abbreviations: *UA*, Unstable angina; *NSTEMI*, non–ST-elevation myocardial infarction; *MI*, myocardial infarction; *CABG*, coronary artery bypass grafting; *GFR*, glomerular filtration rate; *CT*, computed tomography.
* Exercise echo testing was not reimbursed by national insurance system during the study period in Japan.

categorical covariates, and the unpaired *t* test or Wilcoxon rank sum test for continuous covariates.

We calculated the predicted probabilities of bleeding and mortality across all PCIs in the US and Japanese registries from the previously published updated NCDR logistic regression models.[4,5] Although the applied models were published in 2013, they were derived and validated from the July 2009 to June 2011 data set (the mortality model) and February 2008 to April 2011 data set (the bleeding model), which roughly correspond to the data enrollment period for the Japanese data set. All variables for the mortality model were mutually available in the NCDR and JCD. As for the bleeding model, because the JCD did not include the subcategorization of cardiogenic shock (eg, sustained shock) as a variable, the model was reconstructed with the three related variables (sustained shock and salvage, sustained shock or salvage, and transient shock but not salvage) converted to shock and salvage, and shock but not salvage. These probabilities were summed for each PCI category to estimate the risk-adjusted bleeding or mortality rate. In terms of the category of PCI, the observed number of events (O) was divided by the risk-adjusted expected number of events (E) to produce observed-to-expected (O/E) mortality and bleeding ratios. An O/E ratio of 1.0 indicates that the number of observed events equals the number of expected events. Observed and expected ratios <1.0 indicate better than expected outcomes, whereas ratios >1.0 indicate worse than expected outcomes. In addition, the performance of the validated NCDR models was tested for mortality.[6] The model discrimination was assessed using the *c* index; a model with a *c* index >0.70 is generally considered to have acceptable discriminatory capacity. Model calibration (to assess the degree to which the observed outcomes were similar to the predicted outcomes from the model across

Table II. Angiographic information according to the indications for PCI in the United States and Japan

	United States				Japan			
	Overall (n = 732,345)	Elective (stable/no angina; n = 232,111)	UA/NSTEMI (n = 394,612)	STEMI (n = 105,622)	Overall (n = 9941)	Elective (stable/no angina; n = 5030)	UA/NSTEMI (n = 2631)	STEMI (n = 2288)
Cardiogenic shock within 24 h	1.1	0.2	0.7	4.8	2.2	0.3	2.4	7.6
Access Site								
Femoral	95.4	94.8	95.3	97.1	65.6	57.9	64.2	84.0
Radial	4.2	4.8	4.3	2.5	31.8	38.9	33.0	14.9
Brachial	0.4	0.4	0.4	0.3	2.3	2.8	2.4	0.9
Fluoroscopy time	14.4 ± 11.5	14.6 ± 12.2	14.5 ± 11.5	13.3 ± 10.2	29.7 ± 21.5	31.7 ± 23.8	29.1 ± 19.6	26.0 ± 17.1
Use of IABP	2.0	0.5	1.3	8.4	6.3	1.8	6.7	15.6
Use of LV assist device	–	–	–	–	0.3	0.1	0.2	0.8
Multivessel disease	52.5	49.1	54.3	53.3	68.9	70.1	72.8	61.6
No. of diseased vessels								
1	46.5	49.7	44.7	46.3	31.1	29.9	27.2	38.4
2	31.0	30.2	31.2	32.3	44.4	45.6	47.2	38.5
3	21.5	18.9	23.2	21.0	24.5	24.5	25.6	23.1
Multivessel PCI	13.6	15.1	14.9	5.6	10.5	11.4	12.6	6.0
Number of intervened vessels								
1	86.1	84.7	84.9	94.2	89.4	88.5	87.4	93.8
2	12.9	14.3	14.1	5.4	9.4	10.4	11.1	5.4
3	0.7	0.8	0.8	0.2	1.1	1.0	1.5	0.6
Highest-risk lesion								
CTO	3.2	3.4	2.7	4.8	6.4	9.9	4.0	1.2
Bifurcation lesion	12.7	12.4	13.1	12.3	26.1	27.3	26.4	23.0

Abbreviations: *UA*, Unstable angina; *NSTEMI*, non–ST-elevation myocardial infarction; *IABP*, intra-aortic balloon pump; *LV*, left ventricular.

the patients) was performed for the model, with acceptable discriminatory capacity. The calibration was examined by comparing the observed with the predicted average within each of the 10 equal-sized subgroups arranged in increasing order of patient risk.

The authors are solely responsible for the design and conduct of this study, the drafting and editing of the manuscript, and its final contents.

Results

The percentages of PCI performed on an elective basis, for unstable angina/non-ST-elevation myocardial infarction, and for ST-elevation myocardial infarction (STEMI) were 48.7%, 27.1%, and 24%, respectively, in the Japanese cohort, and 31.7%, 53.9%, and 14.4% in the US cohort. The baseline characteristics of the patients, organized according to the indication for PCI, are summarized in Table I. The Japanese cohort was significantly older (mean age 67.9 ± 10.8 vs 64.6 ± 12.1 years, $P < .001$) and comprised a higher prevalence of men, diabetes (including insulin-dependent diabetes), and smoking. Moreover, Japanese patients had a lower body mass index (BMI; 24.2 ± 3.6 vs 30.0 ± 6.4 kg/m^2, $P < .001$), lower prevalence of peripheral vascular disease, and lower prevalence of chronic obstructive pulmonary disease. Other demographic characteristics, as well as the prevalence of comorbidities, were broadly comparable between the Japanese and US cohorts.

Table I also depicts the incidence of preprocedural noninvasive testing. Although the overall percentages of patients who underwent noninvasive testing were similar (~35%), the type of study significantly differed between the 2 countries. Nuclear imaging was the dominant testing modality in the United States, whereas coronary computed tomography was the most frequently performed test in Japan (18.2% vs 1.0%, $P < .001$ [Japan vs US, respectively]), followed by nuclear imaging (16.5% vs 26.7%, $P < .001$) and regular exercise treadmill testing (8.8% vs 3.4%, $P < .001$).

During the study period, most of the US patients underwent PCI via the femoral approach (95.4%); in Japan, a significantly higher number of patients underwent PCI via the radial approach (31.8%). The higher percentage of the radial approach in Japan was consistent for all indications for PCI, ranging from 14.9% for STEMI and up to 38.9% for elective procedures. Angiographically (Table II), compared with the US patients, Japanese patients had a higher rate of complex type lesions such as multivessel disease (68.9% vs 53.5%, $P < .001$), chronic total occlusions (CTOs; 6.4% vs 3.2%, $P < .001$), and bifurcation lesions (26.1% vs 12.7%, $P < .001$). Likely related to these angiographic characteristics, there was a significantly longer average fluoroscopy

Table III. Prescription rate of discharge cardiac medications according to the indications for PCI in the United States and Japan

	United States				Japan			
	Overall (n = 732,345)	Elective (stable/no angina; n = 232,111)	UA/NSTEMI (n = 394,612)	STEMI (n = 105,622)	Overall (n = 9941)	Elective (stable/no angina; n = 5030)	UA/NSTEMI (n = 2631)	STEMI (n = 2288)
Antiplatelet agents								
Aspirin (%)	95.9	96.1	96.1	94.8	96.3	97.2	96.5	94.1
Clopidogrel (%)	88.7	90.2	89.2	83.6	88.3	88.3	88.7	87.9
Prasugrel (%)*	7.3	6.1	7.2	10.2	–	–	–	–
Ticlopidine (%)	0.4	0.4	0.4	0.3	3.8	5.0	3.8	1.2
Cilostazol (%)	–	–	–	–	2.1	2.7	1.5	1.5
β-Blockers (%)	82.5	76.2	83.9	91.6	67.5	64.3	63.8	78.9
Calcium blockers (%)	–	–	–	–	31.6	37.9	34.5	14.2
Statins (%)	87.2	85.3	87.5	90.3	82.2	81.1	82.0	84.7

Abbreviations: *UA*, Unstable angina; *NSTEMI*, non–ST-elevation myocardial infarction.
*Prasugrel was not available in Japan during the study period.

Table IV. In-hospital mortality and complication rates according to the indications for PCI in the United States and Japan

	United States				Japan			
	Overall (n = 732,345)	Elective (stable/no angina; n = 232,111)	UA/NSTEMI (n = 394,612)	STEMI (n = 105,622)	Overall (n = 9941)	Elective (stable/no angina; n = 5030)	UA/NSTEMI (n = 2631)	STEMI (n = 2288)
Cardiogenic shock (%)	0.8	0.2	0.5	3.1	1.8	0.8	1.3	3.9
Heart failure (%)	0.8	0.3	0.6	2.8	1.8	0.4	1.5	5.2
Stroke (%)	0.2	0.1	0.2	0.5	0.4	0.2	0.5	0.7
Tamponade (%)	0.1	0.1	0.1	0.1	0.3	0.1	0.1	0.7
Blood transfusion (%)	2.5	1.3	2.4	5.2	2.2	1.3	2.7	3.7
Bleeding event rate (%)	1.8	1.1	1.7	3.8	2.9	2.1	3.3	4.4
Bleeding from the access site	0.5	0.4	0.5	0.9	1.0	0.8	1.1	1.1
Bleeding from the nonaccess site	1.3	0.7	1.2	2.9	1.9	1.3	2.2	3.3
In-hospital mortality rate (%)	0.9	0.3	0.7	3.3	1.6	0.4	1.7	4.3

Abbreviations: *UA*, Unstable angina; *NSTEMI*, non–ST-elevation myocardial infarction.

duration in Japan compared with in the United States (29.7 ± 21.5 vs 14.4 ± 11.5 minutes, $P < .001$).

As shown in Table III, most of the enrolled patients were discharged with aspirin and secondary antiplatelet agents (eg, clopidogrel) in both countries. Overall, 80% to 90% of the patients in the United States received β-blockers, as compared with only 60% to 70% of Japanese patients. The prescription rate for statins was high in both countries, ranging from 80% to 90%.

On average, Japanese patients had more periprocedural complications compared with the US patients. In particular, they had higher bleeding complication rates within 72 hours of PCI (2.9% vs 1.8%, $P < .001$). Moreover, Japanese patients had a significantly higher in-hospital mortality rate (1.6% vs 0.9%, $P < .001$), as shown in Table IV.

When the observed event rates were compared with the expected event rates based on the established NCDR risk models, the O/E ratios for in-hospital mortality were constant at around 1.0 (1.002 and 0.921, respectively, for US and Japanese patients) (Table V). When the patients were subcategorized according to the PCI status (elective, acute coronary syndrome, and STEMI), the outcomes for elective and STEMI patients were better and worse, respectively, in the United States, whereas an opposite pattern was observed in Japan. Furthermore, the NCDR in-hospital model showed excellent applicability, with a *c* index value of 0.919 (95% CI 0.899-0.939), and the *c* index for in-hospital mortality was consistent across all PCI indications (Table VI). In contrast, the NCDR bleeding model showed only modest applicability for prediction of bleeding complications, with a *c* index score of 0.662 (95% CI 0.639-0.685). Figures 1 and 2 show the calibrations of the risk models for mortality and bleeding complications, respectively.

Table V. Comparison of the observed in-hospital mortality in the Japanese registry and the corresponding values calculated from the US NCDR model

	O/E ratio for mortality rate calculated from 2013 NCDR mortality model		O/E ratio for bleeding rate calculated from 2013 NCDR bleeding model	
	NCDR registered US patients	Japanese patients	NCDR registered US patients	Japanese patients
Overall	1.002	0.921	0.981	0.467
Elective	0.801	1.000	0.868	0.700
UA/NSTEMI	1.065	0.939	1.024	0.549
STEMI	0.998	0.860	0.989	0.318

Abbreviations: *UA*, Unstable angina; *NSTEMI*, non–ST-elevation myocardial infarction.

Table VI. Performances of the NCDR in-hospital mortality and bleeding models in the Japanese registry

	c Index of 2013 NCDR mortality model for Japanese patients	95% CI
A.		
Overall (n = 9941)	0.919	0.899-0.939
Elective (n = 5030)	0.915	0.821-1.000
UA/NSTEMI (n = 2631)	0.895	0.864-0.926
STEMI (n = 2288)	0.789	0.741-0.838
B.		
Overall (n = 9941)	0.662	0.639-0.685
Elective (n = 5030)	0.664	0.616-0.692
UA/NSTEMI (n = 2631)	0.645	0.600-0.691
STEMI (n = 2288)	0.636	0.589-0.693

Abbreviations: *UA*, Unstable angina; *NSTEMI*, non–ST-elevation myocardial infarction.

Discussion

This study was a direct comparison of patients undergoing PCI in Japan and the United States. Few international comparisons have been performed, with the exceptions of trials, and this study represents a unique effort in using standardized variable definitions among 2 registries to facilitate such comparisons. In the present study, the characteristics of patients undergoing PCI in clinical practice in Japan and the US differed substantially; the Japanese cohort was significantly older, with higher proportions of men, diabetes, and smoking. Moreover, a higher proportion of STEMI patients and, angiographically, higher rate of bifurcation and CTO lesions, as well as a longer procedure time, were observed. Moreover, when the in-hospital outcomes were compared, the Japanese patients had higher mortality and bleeding complication rates; the updated statistical model from the NCDR data applied well for the prediction of mortality but not for bleeding complications, with the model constantly underestimating the bleeding risk.

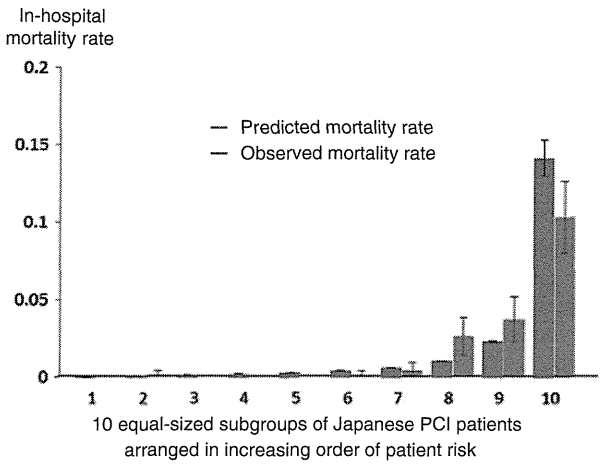
General points about international comparisons

It is important to determine the clinical characteristics and profiles of patients who undergo PCI in different regions, because such data are necessary to evaluate whether patients are being managed appropriately and in line with the available clinical guidelines and evidence-based medicine.The current findings from 2 large-scale registries underscore the importance of establishing clinical registry programs using common data elements/standards in individual regions or countries, because their procedural "culture" may differ substantially. Common data elements within clinical, but not administrative, data would enable specific differences in the patient characteristics and outcomes with adequate risk adjustment. The JCD registry is the first international registry designed prospectively with similar data definitions as those used in the US NCDR (under version 4.0 of the CathPCI Data Collection Form and Data Specifications). As such, it was ideally designed to compare the clinical characteristics of patients undergoing PCI in Japan and the United States. Comparative studies such as the present study can further help evaluate the appropriateness of the procedures and may assist in individual or institutional quality improvements.

Comparisons of the patient background characteristics

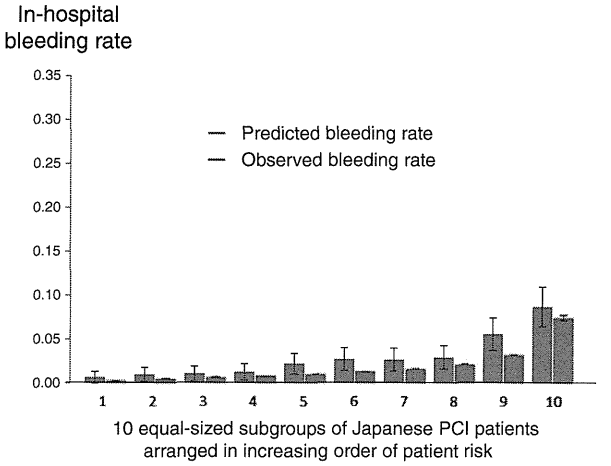
A high number of PCI procedures are performed in Japan every years (>200,000 procedures annually in 2012), but little is currently known about the characteristics of the Japanese patients and how they compare to their counterparts in the United States.[7] In addition, the Asian subgroup in the US registries is relatively small. In our study, most of baseline patient characteristics were comparable between the 2 countries, although the Japanese patients were generally older than the US patients and had a lower burden of predisposing cardiac risk factors. Indirect comparisons of large-scale clinical studies and databases have been performed in the past, and the data from the current study are consistent with these results.[8-11] Lesion complexity, as demonstrated by a higher prevalence of type C, bifurcation, and CTO lesions, was observed more frequently in the PCIs performed in Japan compared with in the United States. Although cardiothoracic surgeons in Japan have comparable surgical skills to their counterparts in the United States,[12] Japanese patients prefer to undergo less invasive procedures. In addition, Japanese patients also have a significantly lower rate of thromboembolic complications, such as stent thrombosis.[13] Of note, the use of dual antiplatelet therapy was applied in 88.3% of our patients in the Japanese data set. This is in concordance with the recent multicenter acute myocardial infarction registry in Japan (J-AMI) study, which demonstrated that clopidogrel loading was used in 79.2% of 2,030 consecutive STEMI patients from 213 Japanese institutions.[14] These numbers are comparable to the use of clopidogrel in the US PCI patients (88.7%).

Figure 1



Calibration of the US mortality model for Japanese PCI patients.

Figure 2



Calibration of the US bleeding model for Japanese PCI patients.

It is of interest that, despite differences in the patient characteristics, the mortality model performed well in this study. Some of the variables seemed to favor US patients (eg, age [64.6 vs 67.9 years] and DM [35.7% vs 42.7%], for the US and Japanese patients, respectively), whereas others favored the Japanese patients (eg, BMI [30.0 vs 24.2 kg/m^2] and other comorbid conditions such as chronic lung disease, peripheral vascular disease, and cerebrovascular disease). It is indeed possible that some of these parameters may have had opposite effects on the observed outcomes. The greater prevalence of diabetes in Japanese patients is in accordance with the rates of diabetes recorded by other coronary artery disease registries in Japan.[13] Moreover, we have previously shown a higher prevalence of DM in Japanese patients compared with in US patients undergoing revascularization procedures during a similar period (prior to the drug-eluting stent era).[9] Interestingly, despite the higher prevalence of DM in Japanese patients, these patients had a better prognosis compared with DM patients in the United States, even after adjustment for known confounding factors. Furthermore, in another previous study by our group, investigating the impact of BMI on procedure-related outcomes,[15] we found that, interestingly, lean patients, rather than obese patients, were at greater risk for in-hospital complications after PCI in Japan. As for the other comorbid conditions, the prevalence of these variables was significantly lower in the Japanese data set compared with in the NCDR data set in the present study (chronic lung disease [14.9% vs 3.1%], peripheral vascular disease [12.4% vs 7.2%], and cerebrovascular disease [12.1% vs 8.1%]) and may have contributed partly, although likely in a very limited amount, to the outcomes of the patients in the Japanese data set.

Comparisons of the outcome information

Comparing clinical outcomes of 2 completely different patient populations remains a challenge, and the evaluation of the applicability of the NCDR risk models in this study was an original approach to circumvent this limitation. The NCDR mortality model performed well when applied to the Japanese cohort. This excellent discrimination appears to be unaffected by the indication of PCI and was evident in all patient subgroups. Our results validate the NCDR in-hospital model as a useful tool in the risk stratification of Japanese patients who undergo PCI under a preformatted clinical registration system and demonstrate that its discrimination is not affected by the international differences of the PCI practice or by its indications.

Interestingly, better outcomes were observed in elective patients in the United States, whereas an opposite pattern was observed in Japanese patients, with a better outcome for STEMI patients rather than elective patients. It has been previously reported that the risk profile is worse for Japanese patients in both the STEMI and elective groups, largely owing to the higher age, higher prevalence of multivessel disease, and higher proportion of patients presenting with cardiogenic shock.[16,17] Of note, there may be some overlap in the risk distributions of the individuals with and without the events. Furthermore, based on the premise that ethnical difference and specific therapeutic measures would reduce the morbidity and mortality, the favorable outcome in Japanese cardiovascular patients together with the use of the radial approach might have contributed to the observed overestimation to some extent. Given the current performance of the NCDR prediction model, minor adjustments in the lowest and/or highest risk category patients may thus be needed.

On the other hand, the discriminatory performance for bleeding complication was suboptimal, and there are several plausible explanations for the limited model discrimination. Asian patients, in general, experience a higher incidence of bleeding complications when treated for cardiovascular conditions in US hospitals,[18,19] and this is also reflected in the constantly higher rate of observed bleeding compared with the predicted bleeding rate in our calibration analysis (Figure 2). Moreover, differences in the sensitivity or availability of antiplatelet or anticoagulation treatments may have led to these differences. For example, glycoprotein IIb/IIIa receptor antagonists and bivalirudin are not available of use in coronary patients in Japan. A previous phase III trial of IIb/IIIa receptors antagonists in Japan showed no improvement in the major cardiac event rates, with increased incidence of bleeding in a dose-dependent manner, whereas bivalirudin has not yet been introduced to the Japanese market.[20] Another possible reason may be related to the fact that the US bleeding model was derived almost exclusively from femoral access patients, whereas about one-third of Japanese patients were treated via the radial access. In addition, the previously stated overreliance on PCI may have affected the predictability of the bleeding model. Increased use of PCI in high-risk, salvage-category patients would naturally reduce the accuracy of the statistical models.

Strengths and limitations

The main strengths of our analysis include the large numbers of participating centers with trained coordinators and patients registered under common variables. The limitations of our analysis are as follows: although the NCDR is a nationwide registry from the United States, the JCD-KiCS is currently only a regional registry, with the recruiting sites mostly based in the Kanto (Tokyo) area of Japan. However, when compared with the national PCI registration data of 2011 (J-PCI; http://www.cvit.jp/registry/progress.html), the patient backgrounds were similar (Supplementary Table II), and our results, hence, seem to carry certain generalizability. At present, the J-PCI only comprises a limited number of variables (14 common variables with the JCD-KiCS) and runs without verification of the registered data; therefore, it cannot be used for international comparisons. Nevertheless, it is under development to incorporate an individual feedback system and auditing in order to further the quality of care among PCI patients in Japan. Second, the reasons for the differences between the 2 populations remain unclear: is it the presentation/progression of coronary artery disease or rather the management and the revascularization strategy of coronary artery disease that are responsible for the observed differences between the 2 countries? Lastly, although our analyses considered several key variables identified from contemporary models developed and validated within national registries, residual confounding is still possible, given the observational nature of the study. For example, the JCD-KiCS does not include the annual operator volume as a variable. Moreover, no procedure-volume analysis has been performed from a Japanese catheter or PCI data set, and it is unclear whether the average annual operator volumes are higher than the international average. This point warrants further investigation, and nationwide registries such as the J-PCI may serve as ideal databases in the future.

Conclusions

In conclusion, data from the JCD registry demonstrated the clinical characteristics of patients who undergo PCI in Japan. Although patients undergoing PCI in Japan differ significantly from those treated in the US, the NCDR mortality model offered useful predictive capacity in Japanese PCI patients as well. On the other hand, the applicability was limited in the bleeding model. This ongoing study will continue to provide valuable information regarding the pathophysiologic, therapeutic, and prognostic issues related to PCI, and this information is expected to aid in conducting safer and more effective PCI treatments.

Acknowledgements

We are indebted to all study coordinators, investigators, and patients who participated in the JCD-KiCS and NCDR CathPCI Registries.

Appendix. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ahj.2015.09.017.

References

1. Bufalino VJ, Masoudi FA, Stranne SK, et al. The American Heart Association's recommendations for expanding the applications of existing and future clinical registries: a policy statement from the American Heart Association. Circulation 2011;123:2167-79.
2. Messenger JC, Ho KK, Young CH, et al. The National Cardiovascular Data Registry (NCDR) data quality brief: the NCDR data quality program in 2012. J Am Coll Cardiol 2012;60:1484-8.
3. Ndrepepa G, Schuster T, Hadamitzky M, et al. Validation of the bleeding academic research consortium definition of bleeding in patients with coronary artery disease undergoing percutaneous coronary intervention. Circulation 2012;125:1424-31.
4. Brennan JM, Curtis JP, Dai D, et al. Enhanced mortality risk prediction with a focus on high-risk percutaneous coronary intervention: results from 1,208,137 procedures in the NCDR (National Cardiovascular Data Registry). J Am Coll Cardiol Intv 2013;6:790-9.
5. Rao SV, McCoy LA, Spertus JA, et al. An updated bleeding model to predict the risk of post-procedure bleeding among patients undergoing percutaneous coronary intervention: a report using an expanded bleeding definition from the National Cardiovascular Data Registry CathPCI registry. J Am Coll Cardiol Intv 2013;6:897-904.

6. Shaw RE, Anderson HV, Brindis RG, et al. Development of a risk adjustment mortality model using the American College of Cardiology–National Cardiovascular Data Registry (ACC-NCDR) experience: 1998-2000. J Am Coll Cardiol 2002;39:1104-12.
7. Park SJ, Kim YH. Current status of percutaneous coronary intervention with drug-eluting stents in asia. Circulation 2008;118:2730-7.
8. Kohsaka S, Goto M, Nagai T, et al. Impact of diabetes among revascularized patients in Japan and the U.S. Diabetes Care 2012;35:654-9.
9. Kohsaka S, Kimura T, Goto M, et al. Difference in patient profiles and outcomes in japanese versus american patients undergoing coronary revascularization (collaborative study by CREDO-Kyoto and the Texas Heart Institute Research Database). Am J Cardiol 2010;105:1698-704.
10. Kimura T, Morimoto T, Nakagawa Y, et al. Antiplatelet therapy and stent thrombosis after sirolimus-eluting stent implantation. Circulation 2009;119:987-95.
11. Kosuge M, Kimura K, Kojima S, et al. Impact of body mass index on in-hospital outcomes after percutaneous coronary intervention for st segment elevation acute myocardial infarction. Circ J 2008;72:521-5.
12. Miyata H, Motomura N, Ueda Y, et al. Effect of procedural volume on outcome of coronary artery bypass graft surgery in Japan: implication toward public reporting and minimal volume standards. J Thorac Cardiovasc Surg 2008;135:1306-12.
13. Toyofuku M, Kimura T, Morimoto T, et al. Three-year outcomes after sirolimus-eluting stent implantation for unprotected left main coronary artery disease: insights from the j-Cypher registry. Circulation 2009;120:1866-74.
14. Nakamura M, Yamagishi M, Ueno T, et al. Current antiplatelet therapy for Japanese patients with ST elevation acute myocardial infarction: J-AMI registry. Cardiovasc Interv Ther 2013;28:162-9.
15. Numasawa Y, Kohsaka S, Miyata H, et al. Impact of body mass index on in-hospital complications in patients undergoing percutaneous coronary intervention in a Japanese real-world multicenter registry. PLoS One 2015;10:e0124399.
16. Kasanuki H, Honda T, Haze K, et al. A large-scale prospective cohort study on the current status of therapeutic modalities for acute myocardial infarction in Japan: rationale and initial results of the HIJAMI registry. Am Heart J 2005;150:411-8.
17. Suzuki M, Sumiyoshi T, Miyachi H, et al. Effect of coronary thrombectomy in cardiogenic shock complicating ST-segment elevation myocardial infarction. Am J Cardiol 2015;115:1649-54.
18. Nasr DM, Brinjikji W, Cloft HJ, et al. Racial and ethnic disparities in the use of intravenous recombinant tissue plasminogen activator and outcomes for acute ischemic stroke. J Stroke Cerebrovasc Dis 2013;22:154-60.
19. Wang TY, Chen AY, Roe MT, et al. Comparison of baseline characteristics, treatment patterns, and in-hospital outcomes of Asian versus non-Asian white Americans with non–ST-segment elevation acute coronary syndromes from the CRUSADE quality improvement initiative. Am J Cardiol 2007;100:391-6.
20. Nakagawa Y, Nobuyoshi M, Yamaguchi T, et al. Efficacy of abciximab for patients undergoing balloon angioplasty: data from japanese evaluation of c7e3 fab for elective and primary PCI organization in randomized trial (JEPPORT). Circ J 2009;73:145-51.

Medicine®

OBSERVATIONAL STUDY

OPEN

Comparison of National Operative Mortality in Gastroenterological Surgery Using Web-based Prospective Data Entry Systems

Takayuki Anazawa, MD, PhD, Jennifer L. Paruch, MD, Hiroaki Miyata, PhD, Mitsukazu Gotoh, MD, PhD, Clifford Y. Ko, MD, MS, MSHS, Mark E. Cohen, PhD, Norimichi Hirahara, PhD, Lynn Zhou, Hiroyuki Konno, MD, PhD, Go Wakabayashi, MD, PhD, Kenichi Sugihara, MD, PhD, and Masaki Mori, MD, PhD

Abstract: International collaboration is important in healthcare quality evaluation; however, few international comparisons of general surgery outcomes have been accomplished. Furthermore, predictive model application for risk stratification has not been internationally evaluated. The National Clinical Database (NCD) in Japan was developed in collaboration with the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP), with a goal of creating a standardized surgery database for quality improvement. The study aimed to compare the consistency and impact of risk factors of 3 major gastroenterological surgical procedures in Japan and the United States (US) using web-based prospective data entry systems: right hemicolectomy (RH), low anterior resection (LAR), and pancreaticoduodenectomy (PD).

Data from NCD and ACS-NSQIP, collected over 2 years, were examined. Logistic regression models were used for predicting 30-day mortality for both countries. Models were exchanged and evaluated to determine whether the models built for one population were accurate for the other population.

We obtained data for 113,980 patients; 50,501 (Japan: 34,638; US: 15,863), 42,770 (Japan: 35,445; US: 7325), and 20,709 (Japan: 15,527; US: 5182) underwent RH, LAR, and, PD, respectively. Thirty-day mortality rates for RH were 0.76% (Japan) and 1.88% (US); rates for LAR were 0.43% versus 1.08%; and rates for PD were 1.35% versus 2.57%. Patient background, comorbidities, and practice style were different between Japan and the US. In the models, the odds ratio for each variable was similar between NCD and ACS-NSQIP. Local risk models could predict mortality using local data, but could not accurately predict mortality using data from other countries.

We demonstrated the feasibility and efficacy of the international collaborative research between Japan and the US, but found that local risk models remain essential for quality improvement.

(*Medicine* 94(49):e2194)

Abbreviations: ACS-NSQIP = American College of Surgeons National Surgical Quality Improvement Program, ASA = American Society of Anesthesiologists, AST = Aspartate aminotransferase, BMI = body mass index, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, LAR = low anterior resection, NCD = National Clinical Database, PD = pancreaticoduodenectomy, PT-INR = prothrombin time–international normalized ratio, RH = right hemicolectomy, SIRS = systemic inflammatory response syndrome, US = United States.

INTRODUCTION

Improving the quality of surgical procedures is dependent on the collection of accurate data. The National Clinical Database (NCD) in Japan was developed in collaboration with the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP), with a shared goal of creating a standardized surgery database for quality improvement. NCD and ACS-NSQIP have developed systems using standardized variable definitions to collect data on risk factors and outcomes after surgery. These databases collect prospective rather than retrospective data. Both use web-based data collection software, contributing to effective quality improvement, via benchmarking and risk-adjusted feedback reports to hospitals; this enables the identification of specific problems and works towards their improvement. The ACS initiated ACS-NSQIP in 2006 and demonstrated improved surgical outcomes among participating private sector hospitals.[1] More than 500 hospitals participated in ACS-NSQIP. NCD in Japan, which was launched in 2010, is a nationwide prospective registry linked to the surgical board certification system. NCD systematically collects accurate data on structures, processes, and outcomes, to develop a standardized surgery database for quality improvement and healthcare quality evaluation.[2] NCD contains the records of >1,200,000 surgical cases collected in 2011, with approximately 4000 institutions participating in 2013.

One of the important advantages of NCD and ACS-NSQIP is the ability to benchmark and compare risk-adjusted outcomes. This ability allows fair comparisons to be made along with collaborative learning. International collaboration is

Editor: Maria Kapritsou.
Received: August 3, 2015; revised: November 5, 2015; accepted: November 7, 2015.
From the Member of Database Committee of Japanese Society of Gastroenterological Surgery (TA, GW); Division of Research and Optimal Patient Care, American College of Surgeons, Chicago, IL (JLP, CYK, MEC, LZ); National Clinical Database, Tokyo, Japan (HM, MG, NH, HK); and Japanese Society of Gastroenterological Surgery, Tokyo, Japan (HM, MG, HK, KS, MM).
Correspondence: Mitsukazu Gotoh, The Japanese Society of Gastroenterological Surgery, 104-0041 Chuouku Sintomi 1-14-1 Central East Building 5F, Tokyo, Japan (e-mail: mgotoh@fmu.ac.jp).
Funding: This study is partially supported from the Ministry of Health, Labour and Welfare, Japan.
Conflict of interest disclosures: The authors report no conflicting financial interests.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000002194

important in healthcare quality evaluation and produces meaningful results; however, few international comparisons of general surgery outcomes using clinical registry data have been accomplished. There is a lack of data regarding outcomes of Japanese patients undergoing gastroenterological surgery and comparison with the United States (US). Furthermore, predictive model application for clinical risk stratification has not been internationally evaluated. Differences in the prevalence of patient comorbidities and their association with outcomes remain unknown. The purpose of this study was to compare patient characteristics; procedure details; operative outcomes; the consistency and impact of risk factors for 3 major gastroenterological surgery procedures: right hemicolectomy (RH), low anterior resection (LAR), and pancreaticoduodenectomy (PD) in Japan and US; and to examine whether risk prediction models built for one population were accurate for the other population. To the best of our knowledge, this is the first study to use large, high-quality data from different patient populations.

METHODS

Study Design and Outcomes

Patient cohorts and risk subcategories for RH, LAR, and PD were selected from both NCD/Japan and ACS-NSQIP/US data. Univariate analysis of each selected predictors for the 3 procedures was conducted for both datasets. Subsequent multivariate models were separately constructed using data from NCD and ACS-NSQIP. Finally, risk models were exchanged and evaluated to determine whether risk prediction models built for one population were accurate for the other population.

Data from NCD and ACS-NSQIP collected over 2 years (2011–2012) were examined. The primary outcome measure of this study was 30-day mortality. Thirty-day mortality was defined as death within 30 days after the operation date regardless of whether the patient had been discharged from initial admission.

Data Acquisition and Patient Selection

The NCD project was approved on November 2010 by the Japan Surgical Society Ethics Committee. The developmental history and current status of the NCD, including sampling strategy, data abstraction procedures, variables collected, outcomes, and structure, are described elsewhere.[2,3] NCD recruits individuals to approve the inputted data from members of various departments in charge of annual cases, as well as data entry officers through a web-based data management system to assure the traceability of the data. NCD conducted onsite audits using source data randomly for mortality, and the results were found to be accurate. Currently, NCD is planning to perform onsite and remote audit for verifying the accuracy of existing data for morbidities. The ACS-NSQIP program and dataset have been described elsewhere.[4,5] Data are abstracted by trained Surgical Clinical Reviewers using standardized definitions, including patient demographics, comorbidities, laboratory values, operative variables, and complications.

Patients who underwent RH, LAR, and PD were identified using Current Procedural Terminology (CPT) (US) and NCD codes (Japan). Both NCD and ACS-NSQIP contain patient cohorts limited to malignant tumor patients only. Any records with entry denied by patients were excluded from this analysis. Records with missing information regarding age, sex, or status at 30 days postoperation were also excluded. For the PD procedure, we excluded cases with simultaneous major hepatectomy.

All variables, definitions, and inclusion criteria in NCD/Japan are accessible on the NCD website (http://www.ncd.or.jp/). Descriptions of the qualifications, auditing of data collection personnel, case inclusion criteria, sampling data collection strategy, and variable and outcome definitions in ACS-NSQIP/US are available online in ACS-NSQIP user guide.[6]

Variables

Two sets of predictive variables were constructed from the NCD/Japan and ACS NSQIP/US data fields. Patient demographic variables considered were age and sex. General factors considered were as follows: preoperative functional status (independent, partially dependent, or totally dependent); American Society of Anesthesiologists (ASA) class; dyspnea (none, moderate exertion, or at rest); emergency cases; and body mass index (BMI: normal, underweight, overweight, and 3 categories of obesity). ASA class was not considered in further multivariate analysis because the criterion to determine class was inconsistent between countries. Comorbidities included were diabetes (oral medication or insulin-dependent); a history of chronic obstructive pulmonary disease (COPD); hypertension requiring medication; congestive heart failure; bleeding disorders; sepsis (systemic inflammatory response syndrome, sepsis, and septic shock); disseminated cancer; chronic kidney disease (CKD) stage; and weight loss (>10% in previous 6 mo). Length of hospital stay was also compared.

Preoperative laboratory variables examined included albumin, white blood count, prothrombin time-international normalized ratio (PT-INR), total bilirubin, and aspartate aminotransferase (AST). Missing laboratory data continued as separate categories. It should be noted that missing values are virtually nonexistent for predictors, except for laboratory variables, where clinical issues have a substantial impact on the ordering of tests.

Statistical Analysis

Raw frequencies and chi-square tests were used to assess differences in the distribution of general factors, comorbidities, and laboratory values, as well as their association with 30-day mortality. Because of the low number of deaths, the risk models were developed with a limited number of variables.[7] To identify these variables, we first used a logistic regression technique with forward selection to identify the most significant predictor variables. Sharing the same SAS code, we generated 3 models (1 for each surgical group) in each country, with lists of the top predictors (data not shown). We used these lists to select a common set of predictors to be used in the final risk models. For the final risk models, logistic regression techniques with forced selection were used to develop models that predict 30-day mortality using a set of relevant comparably defined risk factor variables in both countries. Model fit was assessed using Hosmer–Lemeshow goodness-of-fit statistic for calibration and c-statistic for discrimination.[8,9] The c-statistic allows model discrimination to be measured, with 1.0 indicating perfect discrimination and 0.5 being no better than chance. These models were then used to predict mortality using data from the other dataset (ie, the NCD model was used to predict mortality using the ACS-NSQIP data and vice versa). Observed and expected mortality rates were compared. All data manipulation and analysis were performed with SAS version 9.3 (SAS Institute Inc.).

RESULTS

Risk Profiles and Outcomes

During the study period, a total of 50,501 patients underwent RH (Japan, 34,638; US, 15,863), 42,770 patients underwent LAR (Japan, 35,445; US, 7325), and 20,709 patients underwent PD (Japan, 15,527; US, 5182). Thirty-day unadjusted mortality rates for RH were 0.76% in Japan and 1.88% in US; mortality rates for LAR were 0.43% in Japan and 1.08% in US; and mortality rates for PD were 1.35% in Japan and 2.57% in US. The risk profiles and outcomes of each procedure from both databases are described in Table 1 (RH), Table 2 (LAR), and Table 3 (PD). The ACS-NSQIP population for each procedure tended to be younger. When we looked at the 30-day mortality associated with age, we observed that in both countries, mortality increases as age increases; however, the effect was more pronounced in the ACS-NSQIP data. Laparoscopy was conducted in 36.6% of the Japanese and 56.9% of the US RHs, and 42.9% of the Japanese and 44.2% of the US LARs. Notably, the percentage of patients with a high BMI substantially differed between cohorts. The ACS-NSQIP cohort had a significantly shorter length of hospital stay. The prevalence of patients with CKD differed between Japan and US. Univariate analysis revealed the patient risk factors that were significant predictors of mortality after RH, LAR, and PD (Tables 1–3).

The Risk Models for Mortalities

The final logistic model for 30-day mortalities of each procedure, along with odds ratios (ORs) and 95% confidence intervals (CIs), is presented in Table 4. For RH, 14 significant risk factors for 30-day mortality were identified in Japan, and, in contrast, 17 significant risk factors were identified in US. The c-statistic was calculated to evaluate model performance. The c-statistic was 0.857 for the Japan model and 0.840 for the US model, indicating adequate discrimination. The Hosmer–Lemeshow statistic was 11.243 ($P = 0.19$) for the Japan model and 5.8660 ($P = 0.66$) for the US model, indicating both models adequately assigned risk. For LAR, 12 significant risk factors for 30-day mortality were identified in Japan; in contrast, 10 significant risk factors were identified in US. The c-statistic was 0.782 for the Japan model and 0.822 for the US model, indicating adequate discrimination. The Hosmer–Lemeshow statistic was 5.2355 ($P = 0.63$) for the Japan model and 10.9464 ($P = 0.20$) for the US model, indicating both models adequately assigned risk. For PD, 9 significant risk factors for 30-day mortality were identified in Japan; in contrast, 11 significant risk factors were identified in US. The c-statistic was 0.684 for the Japan model and 0.719 for the US model, indicating good discrimination. The Hosmer–Lemeshow statistic was 9.908 ($P = 0.27$) for the Japan model and 8.6192 ($P = 0.38$) for the US model, indicating both models adequately assigned risk. ORs for each variable were similar between countries.

Exchange Each Risk Model

Models were exchanged between countries and were used to create new models with forced selection to evaluate model transferability (Table 5). For RH, the c-statistic was 0.789 based on US data using the Japan model formula and 0.828 based on Japanese data using the US model formula, indicating adequate but decreased discrimination. The Hosmer–Lemeshow statistic was 171.01 ($P < 0.001$) based on US data using the Japan model formula and 955.23 ($P < 0.001$) based on Japanese data using the US model, indicating neither model adequately assigned risk. For LAR, the c-statistic was 0.786 based on US data using the Japan model formula and 0.778 based on Japanese data using the US model formula, indicating good but decreased discrimination. The Hosmer–Lemeshow statistic was 49.54 ($P < 0.001$) based on US data using the Japan model formula and 145.37 ($P < 0.001$) based on Japanese data using the US model, indicating neither model adequately assigned risk. For PD, the c-statistic was 0.674 based on US data using the Japan model formula and 0.540 based on Japanese data using the US model formula, indicating inadequate discrimination. The Hosmer–Lemeshow statistic was 8.8173 ($P = 0.36$) based on US data using the Japan model formula and 366.22 ($P < 0.001$) based on Japanese data using the US model. In all three procedures, we ran each risk model using the other country's data to assess the discrimination of each model.

Observed and Expected Mortality

Both NCD and ACS-NSQIP models were able to predict the number of deaths in the Japan dataset accurately. However, we decreased accuracy when using models from one country's dataset to predict the number of deaths in the other; we sound the ACS-NSQIP model overpredicted deaths in the NCD dataset, whereas the NCD model underpredicted deaths in the ACS-NSQIP dataset (Table 5). Figures 1 and 2 show the 30-day mortality model calibrations and observed event rates versus predicted rates. In measures of calibration (Hosmer–Lemeshow plots), the y axis gives the predicted number of deaths, and the x axis gives the actual number of deaths observed, that is, a perfect straight line would be a perfect model. Risk models based on local data accurately predicted mortality rates; however, risk models based on the other country's data could not accurately predict mortality rates.

DISCUSSION

Our study is the first international comparison of nationwide operative mortality in gastroenterological surgery using similar web-based prospective data entry systems, with collaboration between the NCD/Japan and the ACS-NSQIP/US. Although some international comparative studies provided variations in mortality rate between countries,[10,11] these studies were under the restriction of the inherent differences in the data collection methods between the datasets. Also, these studies did not examine whether risk prediction models built for one population were accurate for the other population. ACS-NSQIP participation have not offered a clear mechanism for quality improvement[12,13]; however, these are undeniably considered the highest clinical quality standards for evaluating risk-adjusted surgical outcomes. Both use rigorous, standardized data collection methods. Preoperative variables are clearly defined with the same definitions used in both databases and the same defined data collection methodology, including a strict follow-up period for outcomes.[2,14] By comparing the 2 datasets, we found differences in the following: descriptive data including preoperative patient variables; definitions and interpretation of ASA classifications; missing data from preoperative blood tests; duration of hospital stay after surgery; and 30-day mortality. We then created risk models based on local data for each country to predict mortality after each procedure. We found that although the exchanged models had adequate discrimination for mortality after each procedure, the models failed to yield adequate calibration between countries. This finding clearly indicated that risk models based on local data remain essential for quality assessment and improvement.