TABLE 1. Patient characteristics of the original and matched cohorts

Variable	Original cohort ONCAB (n = 1134)	Original cohort OPCAB (n = 1053)	Original cohort *P* value	Matched cohort ONCAB (n = 918)	Matched cohort OPCAB (n = 918)	Matched cohort *P* value
Ejection fraction (%)	26.6 ± 10.4	27.2 ± 7.9	.159	26.8 ± 11.1	27.0 ± 7.8	.734
Age (yrs)	65.7 ± 10.2	67.4 ± 10.1	.002	66.7 ± 9.8	66.2 ± 10.0	.281
Male sex	978 (86.2)	903 (85.8)	.742	784 (85.4)	786 (85.6)	.895
Body mass index	23.0 ± 3.7	22.9 ± 3.8	.417	22.9 ± 3.7	23.0 ± 3.8	.557
Smoking history	742 (65.4)	701 (66.6)	.574	592 (64.5)	610 (66.4)	.377
Diabetes	731 (64.5)	633 (60.1)	.036	574 (62.5)	581 (63.3)	.735
Hyperlipidemia	669 (59.0)	571 (54.2)	.025	517 (56.3)	520 (56.6)	.888
Hypertension	835 (73.6)	758 (72.0)	.387	668 (72.8)	669 (72.9)	.958
Serum creatinine (mg/dL)	2.19 ± 3.42	1.96 ± 2.47	.072	2.13 ± 3.54	2.01 ± 2.53	.403
Preoperative eGFR (mL/min/1.73 m^2)	39.0 ± 21.0	39.9 ± 21.5	.333	39.3 ± 20.6	40.1 ± 22.0	.381
Preoperative dialysis	160 (14.1)	128 (12.2)	.177	117 (12.7)	120 (13.1)	.835
Cerebrovascular disease	150 (13.2)	182 (17.3)	.008	133 (14.5)	131 (14.3)	.894
Carotid stenosis	73 (6.4)	94 (8.9)	.028	61 (6.6)	78 (8.5)	.134
Chronic lung disease	120 (10.6)	148 (14.1)	.013	105 (11.4)	95 (10.3)	.454
Extracardiac vascular disease	212 (18.7)	223 (21.2)	.146	176 (19.2)	174 (19.0)	.905
Prior percutaneous coronary intervention	279 (24.6)	263 (25.0)	.840	229 (24.9)	225 (24.5)	.829
Prior myocardial infarction	693 (61.1)	615 (58.4)	.197	543 (59.2)	547 (59.6)	.849
Congestive heart failure	511 (45.1)	426 (40.5)	.030	385 (41.9)	386 (42.0)	.962
Unstable angina	355 (31.3)	321 (30.5)	.678	282 (30.7)	285 (31.0)	.880
Preoperative shock	74 (6.5)	58 (5.5)	.318	55 (6.0)	54 (5.9)	.921
Preoperative arrhythmia	155 (13.7)	127 (12.1)	.262	115 (12.5)	115 (12.5)	1.000
New York Heart Association functional class III or IV	506 (44.6)	392 (37.2)	<.001	370 (40.3)	377 (41.1)	.739
Left main disease ≥50%	405 (35.7)	355 (33.7)	.326	320 (34.9)	326 (35.5)	.769
Triple-vessel disease	955 (84.2)	840 (79.8)	.007	757 (82.5)	764 (83.2)	.665
Aortic stenosis ≥ grade 1	20 (1.8)	32 (3.0)	.05	15 (1.6)	11 (1.2)	.429
Mitral stenosis ≥ grade 1	13 (1.1)	10 (0.9)	.652	11 (1.2)	6 (0.7)	.223
Aortic insufficiency ≥ grade 2	87 (7.7)	108 (10.3)	.034	77 (8.4)	71 (7.7)	.607
Mitral insufficiency ≥ grade 2	326 (28.7)	361 (34.3)	.005	275 (30.0)	272 (29.6)	.878
Tricuspid insufficiency ≥ grade 2	131 (11.6)	144 (13.7)	.135	113 (12.3)	107 (11.7)	.666
Urgent status	191 (16.8)	165 (15.7)	.458	154 (16.8)	148 (16.1)	.706

Data are presented as n (%) or mean ± standard deviation. *ONCAB*, On-pump coronary artery bypass; *OPCAB*, off-pump coronary artery bypass; *eGFR*, estimated glomerular filtration rate.

RESULTS

Patient Characteristics of All Unmatched Patients

Patient characteristics of the entire unmatched cohort are presented in Table 1. The OPCAB group was significantly older and had significantly higher prevalence of cerebrovascular disease, carotid stenosis, respiratory disease, aortic valve insufficiency, and mitral valve insufficiency. However, the ONCAB group had significantly higher prevalence of diabetes mellitus, hyperlipidemia, congestive heart failure, New York Heart Association functional class III or IV, and triple-vessel disease.

Operative Data and Clinical Outcome for the Original, Unmatched Cohort

Table 2 shows operative data for the entire unmatched cohort. The OPCAB group had significantly fewer distal anastomoses but employed both the right and left internal thoracic arteries significantly more frequently. Unplanned conversion from OPCAB to ONCAB occurred in 64 patients (6.1%). Aortic crossclamping was performed in 406 patients (35.8%) in the ONCAB group. In 72.2% of the OPCAB group, proximal anastomosis was performed without aortic clamping (326 patients [31.0%] with aortic no-touch technique and 434 patients [41.2%] with a suture device). Operative durations were significantly shorter in the OPCAB group (316.0 vs 376.3 minutes; $P < .001$).

Several early outcomes were significantly better in the OPCAB group (Table 3), which had significantly lower 30-day mortality and operative mortality and significantly lower incidence of reoperation for bleeding, deep sternal wound infection, prolonged (>24 hours) mechanical ventilation, prolonged (≥8 days) intensive care unit (ICU) stay, and perioperative transfusion. Although the incidence of MACEs was significantly lower in the OPCAB group, the

TABLE 2. Operative data for the original cohort

Variable	ONCAB (n = 1134)	OPCAB (n = 1053)	*P* value
Operative duration (min)	376.3 ± 105.5	316.0 ± 101.3	<.001
CPB time (min)	153.5 ± 59.1	—	—
Distal anastomoses	3.35 ± 1.05	3.15 ± 1.27	<.001
Proximal anastomosis			
Aortic no-touch	114 (10.1)	326 (31)	<.001
Partial clamp	327 (28.8)	269 (25.5)	.084
Suture device	286 (25.2)	434 (41.2)	<.001
Total clamp	406 (35.8)	24 (2.3)	<.001
ITA use			
Left	1031 (90.9)	978 (92.9)	.094
Right	264 (23.3)	404 (38.4)	<.001
Bilateral	245 (21.6)	383 (36.4)	<.001
None	87 (7.7)	57 (5.4)	.033

Data are presented as mean ± standard deviation or n (%). *ONCAB*, On-pump coronary artery bypass; *OPCAB*, off-pump coronary artery bypass; *CPB*, cardiopulmonary bypass; *ITA*, internal thoracic artery.

TABLE 4. Operative data in propensity-matched pairs

Variable	ONCAB (n = 918)	OPCAB (n = 918)	*P* value
Operative duration (min)	375.4 ± 103.8	322.5 ± 101.8	<.001
CPB time (min)	152.1 ± 59.2	—	—
Distal anastomoses	3.34 ± 1.05	3.21 ± 1.26	.019
Proximal anastomosis			
Aortic no-touch	97 (10.6)	278 (30.3)	<.001
Partial clamp	268 (29.2)	235 (25.6)	.084
Suture device	228 (24.8)	381 (41.5)	<.001
Total clamp	325 (35.4)	24 (2.6)	<.001
ITA use			
Left	826 (90.0)	856 (93.2)	.012
Right	208 (22.7)	366 (39.9)	<.001
Bilateral	193 (21.0)	348 (37.9)	<.001
None	80 (8.7)	47 (5.1)	.002

Data are presented as n (%) or mean ± standard deviation. *ONCAB*, On-pump coronary artery bypass; *OPCAB*, off-pump coronary artery bypass; *CPB*, cardiopulmonary bypass; *ITA*, internal thoracic artery.

incidence of stroke, perioperative myocardial infarction, renal failure, and renal failure requiring dialysis did not differ between groups.

Outcomes of Propensity Score-Matched Patients

Baseline characteristics of the matched cohort are shown in Table 1. There were no significant differences in any preoperative factor between the 2 groups.

Table 4 shows operative data for the matched cohort, in which the OPCAB group had slightly fewer distal anastomoses but received bilateral internal thoracic artery grafting significantly more frequently. Aortic crossclamping was performed in 325 patients (35.4%) in the ONCAB group. In 71.8% of the OPCAB group, proximal anastomosis was performed without aortic clamping (278 patients [30.3%] with aortic no-touch technique and 381 patients [41.5%] with a suture device). After matching, operative durations were still significantly shorter in the OPCAB group. Unplanned conversion from OPCAB to ONCAB occurred in 56 patients (6.1%), among whom operative mortality was 12.5% (7 patients). Of these patients with unplanned conversion, 40 (71.4%) were converted to ONCAB because of hemodynamic instability.

After propensity-score matching, several clinical outcomes were still better in the OPCAB group, which had significantly lower 30-day mortality and operative mortality as well as significantly lower incidences of reoperation for bleeding, deep sternal wound infection, prolonged ventilation, prolonged ICU stay, and perioperative transfusion (Table 5). Although the incidence of MACE was lower in the OPCAB group ($P = .008$), the incidence of stroke, perioperative myocardial infarction, renal failure, and renal failure requiring dialysis did not differ between groups. Institutional volume-adjusted analysis confirmed most of the results of primary analysis (Table 6).

TABLE 3. Postoperative outcomes in the original cohort

Outcome	ONCAB (n = 1134)	OPCAB (n = 1053)	*P* value
30-d Mortality	42 (3.7)	20 (1.9)	.011
Operative mortality	67 (5.9)	36 (3.4)	.006
Perioperative myocardial infarction	7 (0.6)	6 (0.6)	.885
Stroke	23 (2.0)	20 (1.9)	.828
Major adverse cardiovascular events*	90 (7.9)	54 (5.1)	.008
Reoperation for bleeding	38 (3.4)	8 (0.8)	<.001
Renal failure	81 (7.1)	61 (5.8)	.201
Dialysis	49 (4.3)	30(2.8)	.065
Mediastinitis	39 (3.4)	20 (1.9)	.026
Septicemia	25 (2.2)	17 (1.6)	.315
Atrial fibrillation	143 (12.6)	135 (12.8)	.883
Perioperative transfusion	898 (79.2)	667 (63.3)	<.001
Prolonged ventilation†	153 (13.5)	84 (8.0)	<.001
ICU stay ≥8 d	200 (17.6)	125 (11.9)	<.001
Readmission within 30 d	28 (2.5)	28 (2.7)	.779

Data are presented as n (%). *ONCAB*, On-pump coronary artery bypass; *OPCAB*, off-pump coronary artery bypass; *ICU*, intensive care unit. *Includes operative mortality, myocardial infarction, and stroke. †Defined as ≥24 hours.

DISCUSSION

The benefit of OPCAB technique in patients with a low EF is still unclear. The recent large randomized controlled trials (the ROOBY and CORONARY trials) did not show improved mortality in the OPCAB groups.[1,2] However, in both studies, patients with an EF <0.35 comprised only a small portion of the entire cohort. In the ROOBY trial patients with a low EF accounted for only 5.7% of the entire cohort,[1] whereas in the CORONARY trial patients with a low EF accounted for only 5.4% of OPCAB group and 5.6% of ONCAB group.[2] Therefore, these randomized controlled trials could not reach definite conclusions about the best strategy for surgical coronary revascularization in

TABLE 5. Postoperative outcomes in propensity-matched pairs

Outcome	ONCAB (n = 918)	OPCAB (n = 918)	*P* value
30-d Mortality	34 (3.7)	16 (1.7)	.010
Operative mortality	56 (6.1)	30 (3.3)	.006
Perioperative myocardial infarction	7 (0.8)	6 (0.7)	.781
Stroke	19 (2.1)	14 (1.5)	.380
Major adverse cardiovascular event*	76 (8.3)	43 (4.7)	.002
Reoperation for bleeding	32 (3.5)	8 (0.9)	.001
Renal failure	68 (7.4)	56 (6.1)	.264
Dialysis	40 (4.4)	28 (3.1)	.138
Mediastinitis	31 (3.4)	17 (1.9)	.041
Septicemia	22 (2.4)	14 (1.5)	.178
Atrial fibrillation	119 (13.0)	114 (12.4)	.726
Perioperative transfusion	727 (79.2)	578 (63.0)	<.001
Prolonged ventilation†	123 (13.4)	75 (8.2)	<.001
ICU stay ≥8 d	159 (17.3)	111(12.1)	.002
Readmission within 30 d	27 (2.9)	26 (2.8)	.889

Data are presented as n (%). *ONCAB*, On-pump coronary artery bypass; *OPCAB*, off-pump coronary artery bypass; *ICU*, intensive care unit. *Includes operative mortality, myocardial infarction, and stroke. †Defined as ≥24 hours.

low-EF patients. In this context, large retrospective studies using appropriate risk-adjustment methods are still required to establish a sound treatment strategy for patients with a low EF undergoing CABG.

The Japanese Association for Thoracic Surgery reported that intended OPCAB is performed in more than 60% of all patients undergoing CABG in Japan.[9] As shown in our analysis, even among CABG patients with left ventricular dysfunction, intended OPCAB accounted for approximately half of this high-risk group. We found that in patients with low EF, OPCAB was associated with significant reductions in 30-day mortality and operative mortality, and with a significantly lower incidence of reoperation for bleeding, mediastinitis, perioperative transfusion, prolonged mechanical ventilation, and prolonged ICU stay. The largest retrospective study of OPCAB in patients with low EF was recently conducted using data from the STS national database and demonstrated the clinical benefit of OPCAB.[8] The present study, which is from Japan, where OPCAB is performed more frequently than in other countries, is the second-largest retrospective study comparing OPCAB and ONCAB in patients with low EF.

TABLE 6. Institutional-volume adjusted odds ratios (ORs) of on-pump coronary artery bypass versus off-pump coronary artery bypass

Outcome	OR (95% confidence interval)	*P* value
30-d Mortality	0.447 (0.238-0.839)	.012
Operative mortality	0.521 (0.326-0.832)	.006
Stroke	0.723 (0.355-1.475)	.373
Reoperation for bleeding	0.247 (0.112-0.546)	.001
Renal failure	0.878 (0.605-1.275)	.264
Dialysis	0.740 (0.447-1.225)	.242
Mediastinitis	0.547 (0.297-1.007)	.053
Prolonged ventilation*	0.582 (0.427-0.793)	.001

*Defined as ≥24 hours.

First, OPCAB significantly reduced 30-day mortality (1.7% in OPCAB vs 3.7% in ONCAB; odds ratio [OR], 0.48) and operative mortality (3.3% in OPCAB vs 6.1% in ONCAB; OR, 0.52) in patients with low EF. This is consistent with the results of the meta-analysis of retrospective studies and the report from the STS national database. In their meta-analysis of 13 retrospective studies that included only patients with poor left ventricular function, Jarral and colleagues[10] reported a 39% reduction in the risk of 30-day mortality in the OPCAB cohort (OR, 0.61). Based on propensity-score analysis using the STS national database, Keeling and colleagues[8] reported that OPCAB was associated with significantly lower in-hospital mortality (adjusted OR, 0.82 in all centers and 0.63 in high-volume centers) in patients with an EF <0.30. Other studies have suggested that the benefit of OPCAB may be more apparent in high-risk patients. Puskas and colleagues[3] reported that there was a significant mortality benefit for OPCAB in patients with STS predicted risk of mortality >0.025 (OR, 0.45; 95% confidence interval, 0.33-0.63). In addition, a report using data from the STS national database to compare outcomes of OPCAB and ONCAB showed that OPCAB was associated with a greater reduction in mortality and morbidity in patients with higher STS predicted risk of mortality scores.[11] These results may explain the risk-reduction benefit of OPCAB in patients with low EF. Preoperative renal function, which is 1 of the strongest prognostic factors, should also be considered when interpreting the risk-reduction benefit of OPCAB that we have demonstrated in the present study. Our cohort had a lower preoperative median estimated glomerular filtration rate value (41.3 mL/min/1.73 m^2 in ONCAB and 41.6 mL/min/1.73 m^2 in OPCAB) and a higher prevalence of preoperative hemodialysis (12.7% in ONCAB and 13.1% in OPCAB) than those reported for the STS database (median estimated glomerular filtration rate, 71.2 mL/min/1.73 m^2 in ONCAB and 69.2 mL/min/1.73 m^2 in OPCAB; prevalence of hemodialysis, 4.5% in ONCAB and 5.4% in OPCAB).[8] Using data from the STS national database, Chawla and colleagues[12] showed that OPCAB was associated with lower mortality in patients with poor preoperative renal function. The high prevalence of chronic kidney disease in our cohort could explain the strong reduction in mortality in OPCAB despite a smaller sample size than that from the STS database.

OPCAB was also associated with a significantly lower incidence of reoperation for bleeding, perioperative transfusion, mediastinitis, prolonged ventilation, and prolonged ICU stay in this high-risk cohort. Avoidance of transfusion is thought to be among the most important benefits of eliminating extracorporeal circulation. Numerous studies have reported the association of OPCAB with

reduced requirement for transfusion in patients with a low EF[8,13,14]; in particular, the well-designed randomized trial of Puskas and colleagues[13] demonstrated that OPCAB reduced the incidence of coagulopathy. Other recent studies have shown that perioperative blood transfusion was significantly associated with increased mortality after CABG.[15,16] This evidence suggests that a reduction in transfusion requirement might explain the reduced mortality in our OPCAB cohort.

In the present study, the OPCAB group had a significantly lower incidence of mediastinitis despite the increased use of bilateral internal thoracic arteries in this group. There are several explanations for this reduction of deep sternal wound infection in OPCAB. First, extracorporeal circulation itself can increase the incidence of mediastinitis. In their multivariate analysis of CABG cases from the STS database, Fowler and colleagues[17] showed that perfusion time longer than 100 minutes was an independent risk factor for major infection. In the present study, both mean perfusion time longer than 150 minutes and perioperative transfusion could explain the increased incidence of mediastinitis in the ONCAB group. Risnes and colleagues[18] reported that the amount of blood transfused was an independent risk factors for mediastinitis (>10 units; OR, 3.96; 95% confidence interval, 1.60-9.60). This could be explained by a decrease in immune function after transfusion.[19]

Although many large, retrospective studies have shown that OPCAB may decrease the incidence of stroke compared with ONCAB,[11,20-23] there was no significant difference in the incidence of stroke between OPCAB and ONCAB in the present study. In a large, prospective study of perioperative stroke in CABG, Tarakji and colleagues[24] reported that intraoperative stroke rates were lowest in OPCAB (0.14%) and on-pump beating-heart CABG (0%) and statistically higher with on-pump arrested-heart CABG (0.50%). In the present study, about 65% of the ONCAB cohort underwent the procedure using the on-pump beating-heart technique, which might reduce the incidence of stroke in the ONCAB cohort. In addition, the rates of stroke in our study (2.1% in ONCAB and 1.5% in OPCAB) are similar to those in the recent study using data from the STS national database (1.9% in ONCAB and 1.3% in OPCAB), but the number of patients with OPCAB in the present study is about one-fifth of those in the study using the STS database.[8] This suggests that the relatively small effect of stroke prevention in our study could not reach significance because of a lack of statistical power. This may partially explain why the previous randomized controlled trials could not show a preventive effect on perioperative stroke, even in high-risk patients.[25,26]

OPCAB patients received slightly but statistically significantly fewer distal anastomoses per patient than ONCAB patients, which is consistent with results of the CORONARY and ROOBY trials.[1,2] Furthermore, in the present study, OPCAB patients received bilateral internal thoracic arteries more frequently than ONCAB patients. This might be explained by the effort in the OPCAB cohort to minimize aortic manipulation as much as possible. In fact, aortic no-touch technique was used in about 30% of the OPCAB cohort in the present study. Siamak and colleagues[27] reported that the use of bilateral internal thoracic arteries had no significant influence on short-term mortality after CABG in patients with low-EF. Hence, more frequent use of bilateral internal thoracic arteries in OPCAB patients would not significantly affect the short-term outcome in the present study. Because long-term follow-up data were not available in the present study, we could not estimate the prognostic effect of slightly fewer distal anastomoses and more frequent use of bilateral internal thoracic arteries in the OPCAB cohort.

In the present study, 56 patients (6.1%) converted from OPCAB to ONCAB. Although this conversion rate was higher than the conversion rate (2.1%) in the general population reported from a national survey in Japan,[9] this was similar to the conversion rate (5.2%) for patients with low EF reported from the STS database.[8] Operative mortality in patients who were converted from OPCAB to ONCAB was very high. Solving the problem of this high mortality with conversion will be necessary to reduce early mortality in OPCAB patients.

The present study has several limitations. First, because of the retrospective nature of this study, propensity-score matching could not completely adjust for potential selection bias. Second, our data on left ventricular function were limited to left ventricular EF, which represents systolic function. No data on left ventricular dimension and diastolic function, which might affect postoperative mortality, were available. Third, because of the lack of long-term data in the present study, our analysis of the clinical benefit of OPCAB technique is limited to short-term outcomes. Finally, we performed the institutional-volume-adjusted analysis but we could not perform the surgeon-volume-adjusted analysis because during 2010 and later (during our study period), the JACVSD served as a part of the NCD and the method of connecting the surgeons and their procedures changed. This change made it impossible to gain data about surgeon volume during the study period. In the previous study from the JACVSD, institutional volume index was significantly associated with 30-day mortality and operative mortality, but on the other hand, the surgeon-volume index was not significantly associated with these outcomes.[28] Therefore we believe the effect of surgeon volume is more limited than the effect of institution volume.

CONCLUSIONS

In patients with an EF <0.30, OPCAB is associated with significantly reduced early mortality and morbidity. Despite the relatively high mortality accompanying unplanned conversion to ONCAB and the importance of solving this problem, OPCAB technique may improve operative outcomes in this high-risk cohort.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: off-pump coronary artery bypass grafting, on-pump coronary artery bypass grafting, left ventricular dysfunction, propensity score

000 Off-pump versus on-pump coronary artery bypass grafting in patients with left ventricular dysfunction

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Off-pump technique may improve operative outcomes in patients with low ejection fraction undergoing coronary artery bypass grafting.

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ORIGINAL ARTICLE
Cardiovascular Intervention

Outcomes of Percutaneous Coronary Intervention Performed With or Without Preprocedural Dual Antiplatelet Therapy

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Background: Preprocedural dual antiplatelet therapy (DAPT) in percutaneous coronary interventions (PCI) has been shown to improve outcomes; however, the efficacy of the procedure and its complications in Japanese patients remain largely unexplored, so we examined the risks and benefits of DAPT before PCI and its association with in-hospital outcomes.

Methods and Results: We analyzed data from patients who had undergone PCI at 12 centers within the metropolitan Tokyo area between September 2008 and September 2013. Our study group comprised 6,528 patients, of whom 2,079 (31.8%) were not administered preprocedural DAPT. Non-use of preprocedural DAPT was associated with death, postprocedural shock, or heart failure (odds ratio [OR]: 1.47, 95% confidence interval [CI]: 1.10–1.96, P=0.009), and postprocedural myocardial infarction (OR: 1.41, 95% CI: 1.18–1.69, P<0.001) after adjusting propensity scores for known predictors of in-hospital complications. Non-use of DAPT was not associated with procedure-related bleeding complications (OR: 0.98, 95% CI: 0.71–1.59, P=0.764).

Conclusions: Approximately one-third of the patients who underwent PCI did not receive preprocedural DAPT despite guideline recommendations. Our results indicate that patients undergoing PCI with DAPT have a lower risk of postprocedural cardiac events without any increased bleeding risk. Further studies are needed to implement the use of DAPT in real-world PCI. (*Circ J* 2015; **79:** 2598–2607)

Key Words: Bleeding; Dual antiplatelet therapy; Japanese; Percutaneous coronary intervention

Dual antiplatelet therapy (DAPT) improves outcomes in patients undergoing percutaneous coronary interventions (PCI), mainly owing to the therapy's antiplatelet effects on different stages of the platelet activation process. Previous studies have shown that preprocedural DAPT significantly reduces major cardiovascular events in patients with ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and planned PCI cases, compared with patients receiving single antiplatelet therapy.[1–3] As a consequence, although there are slight differences in antiplatelet regimens in different guidelines, the guidelines of the American College of Cardiology, American Heart Association, European Society of Cardiology, and Japanese Circulation Society all recommend pre-PCI DAPT as class I.[4–10]

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Although, the enhanced antithrombotic effects of DAPT should provide additional protection against thrombotic events for patients undergoing PCI, DAPT could also increase the risk of bleeding complications. Particularly, the safety of DAPT in an East Asian population vulnerable to bleeding is unknown.[11,12] The current guidelines from the Japanese Circulation Society are based solely on evidence from Western coun-

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Table 1. Baseline Clinical Characteristics of Each Group Based on Preprocedural Antiplatelet Therapy

	Non-DAPT (n=2,079), % (n)	DAPT (n=4,449), % (n)	P value
Age, years (median)	66.5±11.7	67.1±11.7	0.032
50–59	15.2 (315)	18.9 (842)	<0.001
60–69	28.3 (589)	33.7 (1,501)	<0.001
70–79	27.9 (581)	33.9 (1,510)	<0.001
>80	13.6 (282)	13.8 (614)	0.796
Female	24.5 (509)	19.3 (857)	<0.001
BMI	24.1±3.7	24.2±3.3	<0.001
Coronary risk factors			
DM	37.2 (1,642)	37.7 (175)	0.840
DM with insulin	5.3 (111)	5.9 (264)	0.336
Hypertension	63.5 (1,320)	64.7 (2,877)	0.356
Hyperlipidemia	53.3 (1,108)	57.5 (2,557)	0.002
Smoking	35.2 (732)	34.5 (1,534)	0.564
Comorbidities			
CVD	8.4 (175)	7.7 (343)	0.324
COPD	3.0 (62)	2.3 (101)	0.086
CKD stage ≥3	8.8 (182)	12.0 (535)	<0.001
PAD	6.0 (124)	6.0 (267)	0.953
History			
Prior MI	6.6 (137)	6.7 (300)	0.871
Prior HF	6.5 (136)	5.0 (223)	0.012
Prior CABG	4.3 (89)	2.9 (127)	0.003
Presenting status			
CCS class 3/4	24.1 (502)	20.7 (922)	0.002
CCS class 4	12.7 (265)	8.7 (388)	<0.001
HF	14.8 (308)	11.6 (517)	<0.001
NYHA class 3/4	8.3 (172)	6.9 (306)	0.044
Coronary status			
2-vessel disease	33.6 (669)	43.1 (1,916)	<0.001
3-vessel disease	18.9 (392)	23.3 (1,037)	<0.001
LMT stenosis	6.7 (140)	8.4 (372)	0.023
PCI indication			
STEMI <12h	23.6 (491)	20.5 (913)	0.005
STEMI >12h, unstable	5.8 (121)	5.3 (236)	0.393
NSTEMI/UA	31.6 (656)	28.4 (1,265)	0.045
Stable angina	18.2 (379)	24.1 (1,073)	<0.001
Puncture site			
Radial artery	21.0 (437)	35.3 (1,569)	<0.001
Femoral artery	76.2 (1,584)	62.5 (4,449)	<0.001
Drug-eluting stent	52.1 (1,083)	63.0 (2,802)	<0.001
Bare metal stent	29.8 (619)	26.7 (1,186)	0.023
Single stent	41.5 (863)	56.5 (2,513)	<0.001
Multiple stents	40.4 (840)	33.2 (1,447)	<0.001
Single stent length (mm)	20.5±6.1	20.6±6.1	0.791
Multiple stent length (mm)	31.2±6.5	32.8±6.4	0.703

BMI, body mass index; CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; CKD, chronic kidney disease; CVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; DAPT, dual antiplatelet therapy; DM, diabetes mellitus; HF, heart failure; LMT, left main trunk; MI, myocardial infarction; NSTEMI, non-ST-elevation MI; PCI, percutaneous coronary intervention; PAD, peripheral artery disease; STEMI, ST-elevation MI; UA, unstable angina.

tries, and few trial results from studies focusing on East Asian populations are available. Furthermore, the actual bleeding complication rate in Japanese patients who undergo PCI has not yet been determined. Consequently, despite the Japanese guidelines, the use of preprocedural DAPT still varies among Japanese institutions; a single multicenter study from Japan showed that only 66.7% of Japanese patients who had undergone primary PCI for STEMI received preprocedural DAPT.[13]

To the best of our knowledge, no studies have specifically evaluated the risks and benefits of pre-PCI DAPT and the association with in-hospital outcomes in Japan. Therefore, we investigated the prevalence of DAPT use in a multicenter

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

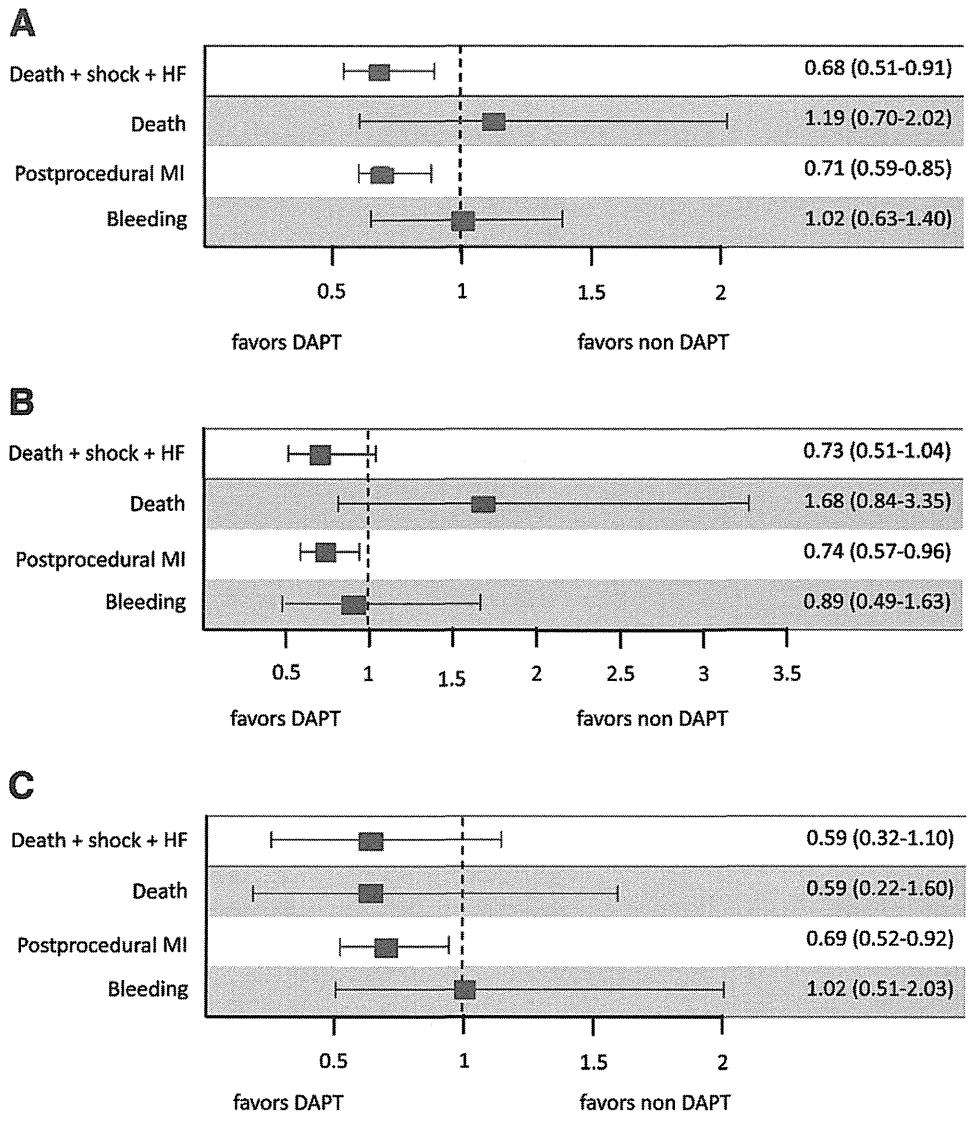

Figure. (**A**) Adjusted in-hospital outcomes. Forest plot of odds ratios (ORs) and 95% confidence intervals (CIs) for in-hospital outcomes among patients who did or did not undergo dual antiplatelet therapy (DAPT) before percutaneous coronary intervention (PCI). (**B**) Adjusted in-hospital outcomes 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 <72 h			
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.

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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.

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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.

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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)

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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

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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