OPEN

In-hospital Bleeding Outcomes of Oral Anticoagulant and Dual Antiplatelet Therapy During Percutaneous Coronary Intervention: An Analysis From the Japanese Nationwide Registry

Fumiaki Yashima, MD, PhD,† Taku Inohara, MD, PhD,†‡ Hiroaki Nishida, MD, PhD,* Kenichiro Shimoji, MD, PhD,* Koji Ueno, MD, PhD,* Shigetaka Noma, MD, PhD,* Kyohei Yamaji, MD, PhD,§ Hideki Ishii, MD, PhD,¶ Nobuhiro Tanaka, MD, PhD,‖ Shun Kohsaka, MD, PhD,† Tetsuya Amano, MD, PhD,** and Yuji Ikari, MD, PhD††*

Abstract: The type of periprocedural antithrombotic regimen that is the safest and most effective in percutaneous coronary intervention (PCI) patients on oral anticoagulant (OAC) therapy has not been fully investigated. We aimed to retrospectively investigate the in-hospital bleeding outcomes of patients receiving OAC and antiplatelet therapies during PCI using Japanese nationwide multicenter registry data. A total of 26,938 patients who underwent PCI with OAC and antiplatelet therapies between 2016 and 2017 were included. We investigated in-hospital bleeding requiring blood transfusion, mortality, and stent thrombosis according to the antithrombotic regimens used at the time of PCI: OAC + single antiplatelet therapy (*double therapy*) and OAC + dual antiplatelet therapy (*triple therapy*). The antiplatelet agents included aspirin, clopidogrel, and prasugrel. The OAC agents included warfarin and direct OACs. Adjusting the dose of OAC or intermitting OAC before PCI was at each operator's discretion. In the study population [mean age (SD), 73.5 (9.5) years; women, 21.5%], the *double therapy* and *triple therapy* groups comprised 5546 (20.6%) and 21,392 (79.4%) patients, respectively. Bleeding requiring transfusion was not significantly different between the groups [adjusted odds ratio (aOR), 0.700; 95% confidence interval (CI), 0.420–1.160; $P = 0.165$] (triple therapy as a reference). Mortality was not significantly different (aOR, 1.370; 95% CI, 0.790–2.360; $P = 0.258$). Stent thrombosis was significantly different between the groups (aOR, 3.310; 95% CI, 1.040–10.500; $P = 0.042$) (triple therapy as a reference). In conclusion, for patients on OAC therapy who underwent PCI, periprocedural triple therapy may be safe with respect to in-hospital bleeding risks. However, further investigations are warranted to establish the safety and efficacy of periprocedural triple therapy.

Key Words: dual antiplatelet therapy, oral anticoagulant, percutaneous coronary intervention, triple therapy

(*J Cardiovasc Pharmacol*™ 2021;78:221–227)

INTRODUCTION

Among patients undergoing percutaneous coronary intervention (PCI), 5%–8% requires oral anticoagulant (OAC) therapy for atrial fibrillation (AF), mechanical heart valves, or venous thromboembolism.[1–5] The bleeding risk among these patients is obviously high because of the simultaneous requirement of OAC and antiplatelet therapies.[2,3] Several randomized controlled trials (RCTs) have consistently demonstrated that compared with triple therapy with OAC and dual antiplatelet therapy (DAPT), double therapy with OAC and single antiplatelet therapy (SAPT) reduced bleeding complications without increasing the risk of ischemic events.[4,6–9] Taking into account these pivotal trials, short-term triple therapy and rapid transition to OAC and SAPT are recommended depending on the bleeding risk in each patient.[1,10–12] Nevertheless, it has not yet been fully investigated which type of periprocedural antithrombotic

Received for publication September 27, 2020; accepted February 2, 2021.

From the *Department of Cardiology, Saiseikai Utsunomiya Hospital, Tochigi, Japan; †Department of Cardiology, Keio University School of Medicine, Tokyo, Japan; ‡Division of Cardiology, Vancouver General Hospital, Vancouver, Canada; §Division of Cardiology, Kokura Memorial Hospital, Kitakyushu, Japan; ¶Department of Cardiology, Fujita Health University Bantane Hospital; ‖Department of Cardiology, Tokyo Medical University Hachioji Medical Center, Tokyo, Japan; **Department of Cardiology, Aichi Medical University, Aichi, Japan; and ††Department of Cardiology, Tokai University School of Medicine, Kanagawa, Japan.

This study was funded by the Grant-in-Aid for Scientific Research from the Japan Agency for Medical Research and Development (grant number 17ek0210097h000) and the Japan Society for the Promotion of Science (grant numbers 16KK0186 and 16H05215). The J-PCI registry is led and supported by the Japanese Association of Cardiovascular Intervention and Therapeutics. The funding sources had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

T. Inohara received a research grant from Boston Scientific. H. Ishii received lecture fees from Astellas Pharma Inc., AstraZeneca Inc., Bayer Pharma Inc., Bristol-Myers Squibb Inc., Chugai Pharma Inc., Daiichi Sankyo Co., Ltd., and Otsuka Pharma Inc. The remaining authors report no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jcvp.org).

Correspondence: Fumiaki Yashima, MD, PhD, Department of Cardiology, Saiseikai Utsunomiya Hospital, 911-1 Takebayashi-cho, Utsunomiya, Tochigi 321-0974, Japan (e-mail: yashima.fumiaki@gmail.com).

regimen, at the time of PCI, is the safest and most effective in patients on OAC therapy.

Periprocedural bleeding events have been reported to be associated with worse long-term prognosis.[13,14] In addition, East Asian patients are more susceptible to bleeding events as known as "East Asian paradox." [15,16] Thus, it is crucial to avoid in-hospital bleeding complications and after discharge, especially in the East Asian cohort.

Therefore, we sought to assess in-hospital bleeding, mortality, and stent thrombosis in patients on OAC therapy according to antithrombotic regimens at the time of PCI, using the Japanese PCI (J-PCI) nationwide registry data.

METHODS

Study Population

The J-PCI registry was established in 2007 and is an ongoing, multicenter, nationwide PCI registry maintained by the Japanese Association of Cardiovascular Intervention and Therapeutics (CVIT) and designed to collect clinical variables and in-hospital outcome data on patients who underwent PCI.[17–23] The CVIT registry subcommittee designed the software for the web-based data collection system, and each data manager in the participating hospitals submits data through this system annually. Registration in the J-PCI database is mandatory for board certification and renewal applications, and although participation in the J-PCI is voluntary, the level of incomplete data is low. According to the annual report of the Japanese Registry on All Cardiac and Vascular Diseases, 773,359 PCI procedures (209,920 for acute manifestations and 563,439 for nonacute manifestations) were performed during the current study period (http://www.j-circ.or.jp/jittai_chosa/, accessed on 14 February 2018). Thus, we included a total of 680,947 PCI procedures; approximately 88% of all procedures in Japan were estimated to be included in our registry. The accuracy of submitted data is maintained by data auditing (20 institutions annually) by members of the CVIT registry subcommittee. This study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and was approved by the institutional committee on human research at our institution. The requirement for acquisition of written informed consent from patients was waived because of the retrospective nature of the study.

We analyzed data from patients who underwent PCI from January 2016 to December 2017 and were registered in the J-PCI. We included all patients treated with OAC before PCI regardless the anticoagulant therapy reasons. In addition, we included both elective and emergent cases, or stable coronary artery disease (CAD) and acute coronary syndrome. Antiplatelet agents in this study included aspirin, clopidogrel, and prasugrel; OAC agents included warfarin and direct oral anticoagulants (DOACs). Ticagrelor was not included because it is uncommon in Japan. There are differences in dosages of antithrombotic agents between Japan and Western countries (see **Tables 1 and 2**, **Supplemental Digital Content 1**, http://links.lww.com/JCVP/A626). The following exclusion criteria were applied: (1) missing data on age and/or sex; (2) very young or very advanced age (<20 or ≥ 100 years); (3) missing data on in-hospital outcomes; (4) taking other antiplatelet and/or anticoagulant agents except aspirin, clopidogrel, prasugrel, warfarin, and DOACs; (5) shock and/or cardiopulmonary arrest on hospital arrival; (6) use of more than one anticoagulant agent; (7) use of more than 2 antiplatelet agents; and (8) without use of any antiplatelet agents (Fig. 1). Afterward, patients on OAC therapy were stratified into the following 2 groups according to antiplatelet therapies at the time of PCI: (1) the double therapy group who received SAPT in addition to OAC for PCI and (2) the triple therapy group who received OAC and DAPT. We assessed clinical outcomes described below between the 2 groups. Adjusting the dose of OAC or intermitting OAC before PCI was at each operator's discretion, and it was not recorded in this study.

Clinical Outcomes

The primary outcome was the in-hospital incidence of bleeding complications, defined as any bleeding event requiring blood transfusion during or after PCI, including access-site and non–access-site bleeding. The detail of bleeding events, such as intracranial bleeding, hemorrhagic stroke, and gastrointestinal bleeding, was not captured. As secondary outcomes, we also evaluated the following: (1) in-hospital mortality and (2) the in-hospital definitive stent thrombosis according to the definition from the Academic Research Consortium.[24] We compared the outcomes and odd ratios (ORs) between the double therapy and triple therapy groups. Differences in the outcomes between warfarin and DOACs were also assessed.

Statistical Analysis

Continuous variables are expressed as mean ± SD and were compared using the Wilcoxon rank-sum test. Categorical variables are presented as percentage and were compared using the χ^2 test. Logistic regression models were used to adjust differences in baseline characteristics between the groups. Covariates for adjustment included sex, age, previous heart failure, heart failure within 24 hours, ST-elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), unstable angina (UA), diabetes mellitus, chronic kidney disease, number of diseased vessels, left anterior descending artery (LAD) and/or left main trunk (LMT) lesions, PCI access site, and DOACs. In addition, in-hospital outcomes were assessed according to the type of OAC (warfarin vs. DOACs) using logistic regression models after including the variable *type of OAC* and the covariates listed above. In all models, institutions were included as a random intercept. All candidate variables had $<1\%$ of missing data. All reported P-values were 2-sided, and a P-value <0.05 was considered statistically significant. All statistical analyses were performed using R statistical software version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

After applying the exclusion criteria, the final study population consisted of 26,938 patients who underwent

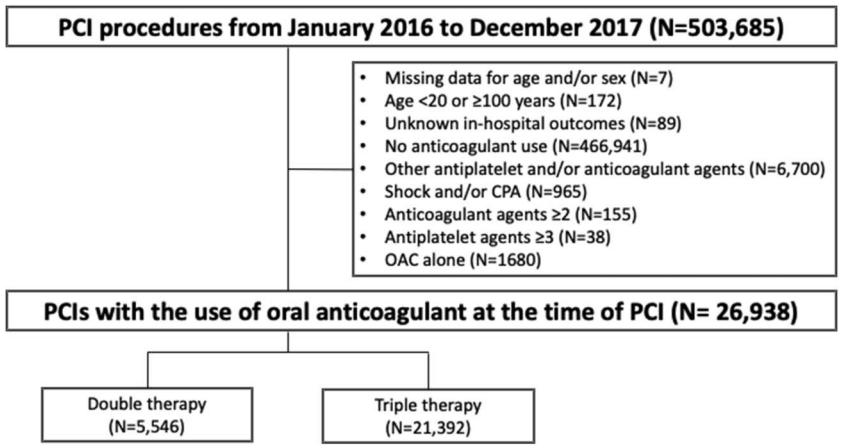

FIGURE 1. Study flow chart. CPA, cardiopulmonary arrest.

PCI and OAC therapy [mean age (SD), 73.5 (9.5) years; female patients, 21.5%]; of these, the double therapy and triple therapy groups comprised 5546 (20.6%) and 21,392 (79.4%) patients, respectively (Fig. 1). The proportions of the 2 groups remained unchanged throughout the study period (see **Figure**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A626).

Baseline characteristics are summarized in Table 1. The average age (74.2 ± 9.6 vs. 73.4 ± 9.5 years, $P < 0.001$) and the proportion of female patients [1240 (22.4%) vs. 4545 (21.2%), $P < 0.001$] were higher in the double therapy group than in the triple therapy group. Stable ischemic heart disease was more frequent in the triple therapy group [4111 (74.3%) vs. 16,676 (78.0%), $P < 0.001$]. LMT lesions were more frequently treated [223 (4.0%) vs. 1026 (4.8%), $P = 0.016$], and graft lesions were less frequently treated [149 (2.7%) vs. 314 (1.5%), $P < 0.001$] in the triple therapy group. The transradial approach was more frequently used in the triple therapy group [3614 (65.2%) vs. 14,332 (67.0%), $P = 0.013$]. Drug-eluting stents were more frequently used in the triple therapy group [4201 (75.7%) vs. 18,173 (85.0%), $P < 0.001$], whereas bare metal stents (BMSs) and drug-coated balloons (DCBs) were more frequently used in the double therapy group [BMSs: 93 (1.7%) vs. 278 (1.3%), P = 0.037; DCBs: 968 (17.5%) vs. 2745 (12.8%), $P < 0.001$]. Details on OAC and antiplatelet agents between the 2 groups are presented in the **Supplemental Digital Content 3** (see **Table 3**, http://links.lww.com/JCVP/A626). Warfarin was used in approximately half of the patients. Aspirin, clopidogrel, and prasugrel were used as SAPT in 55.3%, 31.9%, and 12.8% of patients, respectively. Aspirin and clopidogrel were used as DAPT in 55.9% of patients, whereas aspirin and prasugrel were used as DAPT in the remaining patients.

Clinical Outcomes

Clinical outcomes in the 2 groups are summarized in Table 2. In-hospital bleeding requiring transfusion was not significantly different between the 2 groups [adjusted odds ratio (aOR), 0.700; 95% confidence interval (CI), 0.420–1.160; $P = 0.165$] (triple therapy as a reference). In-hospital mortality was not significantly different (aOR, 1.370; 95% CI, 0.790–2.360; $P = 0.258$), whereas in-hospital stent thrombosis was significantly different between the 2 groups (aOR, 3.310; 95% CI, 1.040–10.500; $P = 0.042$) (triple therapy as a reference).

Comparing warfarin and DOACs, bleeding requiring transfusion was not significantly different (aOR, 1.370; 95% CI, 0.790–2.360; $P = 0.258$) (warfarin as a reference). In-hospital mortality and stent thrombosis were not significantly different between the 2 groups (Table 3). Comparing bleeding requiring transfusion among OACs, and between prasugrel and clopidogrel, in the triple therapy and double therapy groups, there were no significant differences (see **Tables 4–7**, **Supplemental Digital Content 4**, http://links.lww.com/JCVP/A626).

DISCUSSION

We examined the association between antithrombotic regimens at the time of PCI and in-hospital outcomes among patients on OAC therapy using the J-PCI nationwide multicenter registry data. In this study, when compared with periprocedural double therapy, periprocedural triple therapy was not associated with an increased risk of in-hospital bleeding requiring blood transfusion. To the best of our knowledge, this study is the first report to assess in-hospital bleeding outcomes among patients who underwent PCI with OAC therapy according to antiplatelet therapies at the time of PCI.

The WOEST study[6] was the first RCT to demonstrate that compared with triple therapy, double therapy with clopidogrel and warfarin reduced 1-year mortality and bleeding complications after PCI. After the trial, PIONEER AF-PCI trial,[4] RE-DUAL PCI trial,[7] AUGUSTUS,[8] and ENTRUST-AF PCI,[9] which were RCTs investigating the bleeding and mortality risks between triple versus double therapy and between warfarin versus DOACs, have consistently demonstrated that, compared with triple therapy, double therapy with P2Y12 inhibitors and DOAC reduced mortality and bleeding complications after PCI. In addition, very recently a possible benefit of rivaroxaban

TABLE 1. Baseline Characteristics of Patients in the Two Groups

	Double Therapy (n = 5546)	Triple Therapy (n = 21,392)	*P*
Age, yr	74.2 ± 9.6	73.4 ± 9.5	<0.001
Female	1240 (22.4%)	4545 (21.2%)	<0.001
Diabetes mellitus	2533 (45.7%)	10,005 (46.8%)	0.149
Hypertension	4323 (77.9%)	17,019 (79.6%)	0.009
Dyslipidemia	3261 (58.8%)	13,562 (63.4%)	<0.001
Chronic kidney disease	1430 (25.8%)	5819 (27.2%)	0.035
Peripheral artery disease	688 (12.4%)	2565 (12.0%)	0.411
Smoker	1314 (23.7%)	5744 (26.9%)	<0.001
Previous PCI	3194 (57.7%)	11,295 (52.9%)	<0.001
Previous CABG	716 (12.9%)	2018 (9.4%)	<0.001
Previous myocardial infarction	1728 (31.4%)	6587 (31.0%)	<0.001
Previous heart failure	1789 (32.6%)	7595 (35.7%)	<0.001
Clinical presentation			<0.001
Stable ischemic heart disease	4111 (74.3%)	16,676 (78.0%)	
STEMI	347 (6.3%)	1319 (6.2%)	
NSTEMI	205 (3.7%)	639 (3.0%)	
UA	837 (15.1%)	2643 (12.4%)	
Heart failure within 24 h	134 (2.4%)	452 (2.1%)	0.183
Number of diseased vessels			
Single	3439 (62.0%)	12,907 (60.3%)	0.024
Double	1350 (24.3%)	5639 (26.4%)	0.002
Triple	753 (13.6%)	2771 (13.0%)	0.228
Target lesion			
LMT	223 (4.0%)	1026 (4.8%)	0.016
LAD and/or LMT	2736 (49.3%)	10,927 (51.1%)	0.21
RCA	1906 (34.4%)	7014 (32.8%)	0.27
LCX	1439 (25.9%)	5564 (26.0%)	0.928
Graft	149 (2.7%)	314 (1.5%)	<0.001
Access site			0.013
Femoral	1561 (28.1%)	5602 (26.2%)	
Radial	3614 (65.2%)	14,332 (67.0%)	
Others	371 (6.7%)	1458 (6.8%)	
Stents and DCBs			
DES	4201 (75.7%)	18,173 (85.0%)	<0.001
BMS	93 (1.7%)	278 (1.3%)	0.037
DCB	968 (17.5%)	2745 (12.8%)	<0.001

Data are expressed as mean ± SD or number (%).
CABG, coronary artery bypass graft; DES, drug-eluting stent; LCX, left circumflex artery; RCA, right coronary artery.

monotherapy has been reported compared with the combination therapy of rivaroxaban and SAPT in patients with AF and stable CAD, occurring more than 1 year after revascularization or in those with angiographically confirmed CAD not requiring revascularization.[25] Thus, bleeding risk evaluation for each patient and appropriate selection of antithrombotic regimen and duration after PCI in patients on OAC therapy have been emphasized.[1,26]

However, antithrombotic regimens at the time of PCI in patients on OAC therapy have not been fully assessed. The 2016 updated ACC/AHA guideline[11] does not provide an explicit comment regarding this recommended regimen. The 2017 ESC/EACTS guideline,[1] the 2018 updated CCS/CAIC guideline,[10] and the 2018 updated North American expert consensus document[12] conventionally recommend aspirin and clopidogrel administration as DAPT during PCI, even for patients already receiving OAC without providing any relevant evidence as proof. In addition, in the above-mentioned pivotal RCTs, no periprocedural protocols of antithrombotic therapy were designed, and the choice of therapies was at the operators' discretion.[4,6–9] Moreover, it was noted that ischemic events, such as myocardial infarction, stent thrombosis, and cardiovascular death, within a very early period increased numerically in patients without aspirin in ENTRUST-AF PCI, which was consistently observed in the other 3 DOAC AF PCI trials,[9] with the investigators emphasizing that very early withdrawal of aspirin therapy should be performed cautiously.[9] Accordingly, a recent well-documented review suggests keeping the triple therapy only in the periprocedural period and during hospital stay and then dropping aspirin early (ie, before discharge).[27] Our present data regarding periprocedural antithrombotic therapy will be valuable, as our findings will provide some proof for these evidence gaps and support the safety of periprocedural triple therapy as recommended in these updated guidelines and expert consensus documents.

Avoiding in-hospital bleeding associated with PCI is extremely important for both in-hospital and long-term mortality. Patients with periprocedural major bleeding were reported to have increased in-hospital mortality, compared with the control group without bleeding (5.26% vs. 1.87%; $P < 0.001$).[13] The 3-years adjusted hazard ratio for mortality in patients with bleeding within 30 days was reported to be 4.89 (95% CI, 3.08–7.78; $P < 0.001$), compared with those without bleeding.[14] Thus, evidence of periprocedural antithrombotic regimen and bleeding risk is as important as the regimen after PCI.

We speculated the reasons for the insignificant difference in in-hospital bleeding between periprocedural double and triple therapies. One possible reason is that the impact on periprocedural bleeding according to differences in periprocedural antithrombotic regimens might be relatively small in PCI cases with full heparinization. A recent report from the National Cardiovascular Data Registry (NCDR) and the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry indicated that compared with no anticoagulant use, warfarin or DOAC administration was not associated with an increased risk of in-hospital bleeding in patients with myocardial infarction,[28] which is comparable with our result. Another possible reason may be that the insignificant difference was associated with the operators' appropriate bleeding triage and PCI strategy. Bleeding avoidance strategy, such as the transradial approach and use of

TABLE 2. Clinical In-Hospital Outcomes (Double Therapy vs. Triple Therapy)

	Double Therapy (n = 5546)	Triple Therapy (n = 21,392)	*P*	Adjusted ORs	95% CI	*P*
				Double Therapy Versus Triple Therapy (Reference)		
Bleeding requiring transfusion	22 (0.40)	106 (0.50)	0.597	0.700	0.420–1.160	0.165
In-hospital mortality	25 (0.45)	55 (0.26)	0.026	1.370	0.790–2.360	0.258
Stent thrombosis	6 (0.11)	11 (0.05)	0.099	3.310	1.040–10.500	0.042

Data are expressed as number (%). Adjusted ORs and 95% CIs for each outcome were calculated by comparing the double therapy group and the triple therapy group (referent category). Covariables adjusted for were as follows: sex, age, previous heart failure, heart failure within 24 h, STEMI, NSTEMI, UA, diabetes mellitus, chronic kidney disease, number of diseased vessels, LAD and/or LMT lesions, PCI access site, number of antiplatelet agents, and institution (as the random intercept of mixed effects logistic regression). Missing values were not imputed as missing rates were all <1%.

hemostatic devices, might be efficient for reducing access site–related bleeding complications.[29–31] In addition, operators might have adjusted the dose of OAC and administered OAC intermittently before PCI to prevent bleeding events, although intermittent OAC was not recorded in this study. The risk stratification might have led to insignificant difference. Indeed, the 2017 ESC/EACTS guideline and the 2018 updated North American expert consensus document[12] recommend that PT-INR should be in the lower part of the therapeutic range to avoid bleeding complications in patients who underwent PCI and warfarin therapy.[1] 2018 Joint European consensus document says that timely interruption of DOACs (12–24 hours in advance) is preferred.[27,32] However, no standardized blood assay for DOACs is established, and further investigations regarding appropriate adjustment or interruption of DOACs before PCI are required.

This study also investigated differences between in-hospital bleeding outcomes of patients treated with warfarin and DOACs. We expected that DOACs would be associated with a decreased bleeding risk compared with warfarin as observed in PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS. However, there were no significant differences. As mentioned previously, this study did not capture the short interruption of warfarin before PCI. Each operator might have adjusted the warfarin dose and PT-INR or administered warfarin intermittently before PCI to avoid bleeding events. Thus, periprocedural bleeding events because of warfarin might be suppressed. The similar phenomenon was observed in ENTRUST-AF PCI.[9] The rate of the composite of major or clinically relevant nonmajor bleeding within 14 days was numerically—but nonsignificantly—lower with warfarin than with edoxaban. It was assumed that the lower bleeding rate with warfarin might be associated with PT-INR adjustment by each physician; PT-INR at the day of randomization was <2 in 94% of the patients treated with warfarin in the trial.

Prasugrel for patients with ACS was associated with reduced rates of ischemic events but increased risks of bleeding events compared with clopidogrel in the TRIRON-TIMI 38 trial.[32] Given the bleeding risks and "East Asian paradox,[15]" reduced-dose prasugrel (loading dose, 20 mg and maintenance dose, 3.75 mg) has been approved and is used in Japan. It is based on the results of a pivotal RCT in Japan called PRASFIT-ACS.[33] It showed that reduced-dose prasugrel was associated with a lower incidence of ischemic events and similar incidence of bleeding events compared with clopidogrel in patients with ACS. However, 2 recent observational studies from Japan showed higher bleeding risks of prasugrel comparing with clopidogrel in ACS patients.[34,35] In this study including both ACS and non-ACS patients, there were no significant differences regarding bleeding events between prasugrel and clopidogrel. The clinical data regarding prasugrel and clopidogrel in patients with OAC are scarce, and further investigations are warranted.

STUDY LIMITATIONS

This study has several limitations. First, the definition of bleeding complications in this registry differs from the standardized criteria such as those established by the Bleeding Academic Research Consortium.[36] As in the recent consensus document from the Academic Research Consortium for High Bleeding Risk, the bleeding rates varied among previous

TABLE 3. Overall Clinical In-Hospital Outcomes for the Study Population (Warfarin vs. DOACs)

	Warfarin (n = 12,315)	DOACs (n = 14,623)	*P*	Adjusted ORs	95% CI	*P*
				Warfarin Versus DOACs (Warfarin as a Reference)		
In-hospital mortality	47 (0.40)	33 (0.20)	0.026	1.370	0.790–2.360	0.258
Bleeding requiring transfusion	63 (0.51)	67 (0.46)	0.406	0.910	0.620–1.340	0.643
Stent thrombosis	11 (0.09)	6 (0.04)	0.265	0.640	0.190–2.190	0.482

Data are expressed as number (%). Adjusted ORs and 95% CIs for each outcome were calculated by comparing the warfarin group (referent category) and the DOACs group. Covariables adjusted for were as follows: sex, age, previous heart failure, heart failure within 24 h, STEMI, NSTEMI, UA, diabetes mellitus, chronic kidney disease, number of diseased vessels, LAD and/or LMT lesions, PCI access site, number of antiplatelet agents, and institution (as the random intercept of mixed effects logistic regression). Missing values were not imputed as missing rates were all <1%.

studies because of the differences in the definition for bleeding complications.[26] Thus, the incidence of bleeding events was lower in our study because our bleeding definition was confined to requiring blood transfusion, which was clinically relevant.[37,38] Individual bleeding and stroke risk stratification, such as HASBLED and $CHADS_2$ or CHA_2DS_2-VASc scores, were not also recorded in this study. The detail of bleeding events, such as intracranial bleeding, hemorrhagic stroke, and gastrointestinal bleeding, was not captured. Second, the loading and maintenance doses of prasugrel in Japan differ from those in Western countries, whereas those of clopidogrel are the same. Further investigations outside Japan are warranted to corroborate our findings. Third, we did not capture antithrombotic regimens after PCI, ie, how antithrombotic therapy changed after PCI. Fourth, the event number of stent thrombosis was small in this study, and statistical robustness was limited. Fifth, because of the nature of observational studies, unmeasured and/or residual confounders with biased results may exist. We included all patients on OAC because of various indications, such as AF, mechanical heart valves, or venous thromboembolism; however, the frequency of these diagnoses was not recorded in this study. Furthermore, the reasons for double or triple therapy were not captured. Thus, the present analysis included various confounders and biases, and it is possible that our multivariate analyses were not fully adjusted. Sixth, the length of hospitalization and in-hospital follow-up was not captured in this study and it might influence the frequency of the outcomes. Finally, this study only evaluated in-hospital clinical outcomes, as long-term follow-up data were not available. Further investigations (particularly RCTs) with long-term follow-up data and with exclusion of potential confounders and biases are warranted to establish the evidence that periprocedural triple therapy is safe for patients on OAC therapy who are undergoing PCI.

CONCLUSIONS

Compared with periprocedural double therapy, periprocedural triple therapy was not associated with an increased risk of bleeding requiring blood transfusion in patients on OAC therapy who underwent PCI. Periprocedural triple therapy may be safe with respect to in-hospital bleeding risks. However, further investigations are warranted to establish the safety and efficacy of periprocedural triple therapy in PCI patients on OAC therapy.

REFERENCES

1. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2018;39:213–260.
2. Sorensen R, Hansen ML, Abildstrom SZ, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. *Lancet.* 2009;374:1967–1974.
3. Hansen ML, Sorensen R, Clausen MT, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med.* 2010;170:1433–1441.
4. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *New Engl J Med.* 2016;375:2423–2434.
5. Capodanno D, Angiolillo DJ. Triple antithrombotic therapy at the intercept between threats and opportunities: don't throw out the baby with the bath water. *JACC Cardiovasc Interv.* 2017;10:1086–1088.
6. Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet.* 2013;381:1107–1115.
7. Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *New Engl J Med.* 2017;377:1513–1524.
8. Lopes RD, Heizer G, Aronson R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *New Engl J Med.* 2019;380:1509–1524.
9. Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet.* 2019;394:1335–1343.
10. Mehta SR, Bainey KR, Cantor WJ, et al. 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology focused update of the guidelines for the use of antiplatelet therapy. *Can J Cardiol.* 2018;34:214–233.
11. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the Diagnosis and Management of Patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation Acute Coronary Syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation.* 2016;134:e123–e155.
12. Angiolillo DJ, Goodman SG, Bhatt DL, et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention. *Circulation.* 2018;138:527–536.
13. Chhatriwalla AK, Amin AP, Kennedy KF, et al. Association between bleeding events and in-hospital mortality after percutaneous coronary intervention. *JAMA.* 2013;309:1022–1029.
14. Kim YH, Lee JY, Ahn JM, et al. Impact of bleeding on subsequent early and late mortality after drug-eluting stent implantation. *JACC Cardiovasc Interv.* 2011;4:423–431.
15. Levine GN, Jeong YH, Goto S, et al. Expert consensus document: world heart federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. *Nat Rev Cardiol.* 2014;11:597–606.
16. Numasawa Y, Sawano M, Fukuoka R, et al. Antithrombotic strategy for patients with acute coronary syndrome: a perspective from East Asia. *J Clin Med.* 2020;9:1963.
17. Sakakura K, Inohara T, Kohsaka S, et al. Incidence and determinants of complications in rotational atherectomy: insights from the national clinical data (J-PCI registry). *Circ Cardiovasc Interv.* 2016;9:e004278.
18. Numasawa Y, Inohara T, Ishii H, et al. Comparison of outcomes of women versus men with non-ST-elevation acute coronary syndromes undergoing percutaneous coronary intervention (from the Japanese nationwide registry). *Am J Cardiol.* 2017;119:826–831.
19. Inohara T, Kohsaka S, Yamaji K, et al. Impact of institutional and operator volume on short-term outcomes of percutaneous coronary intervention: a report from the Japanese nationwide registry. *JACC Cardiovasc Interv.* 2017;10:918–927.
20. Yamaji K, Kohsaka S, Morimoto T, et al. Relation of ST-segment elevation myocardial infarction to daily ambient temperature and air pollutant levels in a Japanese nationwide percutaneous coronary intervention registry. *Am J Cardiol.* 2017;119:872–880.
21. Ozaki Y, Katagiri Y, Onuma Y, et al. CVIT expert consensus document on primary percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI) in 2018. *Cardiovasc Interv Ther.* 2018;33:178–203.

22. Inohara T, Kohsaka S, Yamaji K, et al. Risk stratification model for in-hospital death in patients undergoing percutaneous coronary intervention: a nationwide retrospective cohort study in Japan. *BMJ Open*. 2019;9: e026683.
23. Sawano M, Yamaji K, Kohsaka S, et al. Contemporary use and trends in percutaneous coronary intervention in Japan: an outline of the J-PCI registry. *Cardiovasc Interv Ther.* 2020;35:218–226.
24. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115: 2344–2351.
25. Yasuda S, Kaikita K, Akao M, et al. Antithrombotic therapy for atrial fibrillation with stable coronary disease. *New Engl J Med.* 2019;381: 1103–1113.
26. Urban P, Mehran R, Colleran R, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention. *Circulation*. 2019;140:240–261.
27. Capodanno D, Huber K, Mehran R, et al. Management of antithrombotic therapy in atrial fibrillation patients undergoing PCI: JACC state-of-the-art review. *J Am Coll Cardiol.* 2019;74:83–99.
28. Feldman DN, Wang TY, Chen AY, et al. In-hospital bleeding outcomes of myocardial infarction in the era of warfarin and direct oral anticoagulants for atrial fibrillation in the United States: a report from the national cardiovascular data registry acute coronary treatment and intervention outcomes network registry. *J Am Heart Assoc.* 2019;8:e011606.
29. Mason PJ, Shah B, Tamis-Holland JE, et al. An update on radial artery access and best practices for transradial coronary angiography and intervention in acute coronary syndrome: a scientific statement from the American Heart Association. *Circulation Cardiovascular Interv*. 2018; 11:e000035.
30. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* 2018;40:87–165.
31. Feldman DN, Swaminathan RV, Kaltenbach LA, et al. Adoption of radial access and comparison of outcomes to femoral access in percutaneous coronary intervention: an updated report from the national cardiovascular data registry (2007–2012). *Circulation*. 2013;127:2295–2306.
32. Lip GY, Collet JP, Haude M, et al. 2018 joint european consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). *Europace.* 2019;21:192–193.
33. Saito S, Isshiki T, Kimura T, et al. Efficacy and safety of adjusted-dose prasugrel compared with clopidogrel in Japanese patients with acute coronary syndrome: the PRASFIT-ACS study. *Circ J.* 2014;78:1684–1692.
34. Akita K, Inohara T, Yamaji K, et al. Impact of reduced-dose prasugrel vs. standard-dose clopidogrel on in-hospital outcomes of percutaneous coronary intervention in 62 737 patients with acute coronary syndromes: a nationwide registry study in Japan. *Eur Heart J Cardiovasc Pharmacother.* 2020;6:231–238.
35. Shoji S, Sawano M, Sandhu AT, et al. Ischemic and bleeding events among patients with acute coronary syndrome associated with low-dose prasugrel vs standard-dose clopidogrel treatment. *JAMA Netw Open*. 2020;3:e202004.
36. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123: 2736–2747.
37. Chan W, Ajani AE, Clark DJ, et al. Impact of periprocedural atrial fibrillation on short-term clinical outcomes following percutaneous coronary intervention. *Am J Cardiol.* 2012;109:471–477.
38. Ndrepepa G, Berger PB, Mehilli J, et al. Periprocedural bleeding and 1-year outcome after percutaneous coronary interventions: appropriateness of including bleeding as a component of a quadruple end point. *J Am Coll Cardiol.* 2008;51:690–697.