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 interrupting 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 (aOR, 0.700; 95% CI, 0.790–0.710). Stent thrombosis was significantly different between the groups (aOR, 1.370; 95% CI, 0.790–2.360; P = 0.258). 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

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.6,7 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.8–10 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
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.\textsuperscript{13,14} In addition, East Asian patients are more susceptible to bleeding events as known as “East Asian paradox.”\textsuperscript{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.\textsuperscript{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 PCI regardless the anticoagulant therapy reasons. 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 two-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...
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 double therapy group [4111 (74.3%) vs. 16,676 (78.0%), P < 0.001]. LMT lesions were more frequently treated [149 (2.7%) vs. 314 (1.5% P < 0.001], 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 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, RE-DUAL PCI trial, AUGUSTUS, and ENTRUST-AF PCI, 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%) | 0.099 |
| 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%)      | 6578 (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%) |       |
| 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 (%).

However, antithrombotic regimens at the time of PCI in patients on OAC therapy have not been fully assessed. The 2016 updated ACC/AHA guideline11 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 document12 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 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 antiplatelet use, warfarin or DOAC administration was not associated with an increased risk of in-hospital bleeding in patients with myocardial infarction, 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 translradial approach and use of 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
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 document12 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 Indeed, the 2017 ESC/EACTS guideline and the 2018 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 inhospital 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 TRITON-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

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

|                            | Double Therapy (n = 5546) | Triple Therapy (n = 21,392) | Adjusted ORs | 95% CI          |
|---------------------------|--------------------------|----------------------------|--------------|-----------------|
| Bleeding requiring transfusion | 22 (0.40)                | 106 (0.50)                 | 0.597        | 0.700           |
| In-hospital mortality      | 25 (0.45)                | 55 (0.26)                  | 0.026        | 1.370           |
| Stent thrombosis           | 6 (0.11)                 | 11 (0.05)                  | 0.099        | 3.310           |

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). Covariates 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%.

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

|                        | Warfarin (n = 12,315) | DOACs (n = 14,623) | Adjusted ORs | 95% CI          |
|------------------------|-----------------------|-------------------|--------------|-----------------|
| In-hospital mortality  | 47 (0.40)             | 33 (0.20)         | 0.026        | 1.370           |
| Bleeding requiring transfusion | 63 (0.51)             | 67 (0.46)         | 0.406        | 0.910           |
| Stent thrombosis       | 11 (0.09)             | 6 (0.04)          | 0.265        | 0.640           |

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. Covariates 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.27,38 Individual bleeding and stroke risk stratification, such as HASBLED and CHADS2 or CHA2DS2-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.

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