Safety and Efficacy of Low-Dose Prasugrel as Part of Triple Therapy With Aspirin and Oral Anticoagulants in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention
— From the TWMU-AF PCI Registry —

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Background: Using the standard maintenance dose of prasugrel (10 mg/day) as part of triple therapy with aspirin and an oral anticoagulant (OAC) is not recommended in the current guidelines because it increases the risk of bleeding compared with clopidogrel. However, the safety and efficacy of low-dose prasugrel (3.75 mg/day) as part of triple therapy has not been reported.

Methods and Results: We registered 816 consecutive patients with atrial fibrillation (AF) who underwent percutaneous coronary intervention (PCI) from January 2011 to June 2016 at 8 hospitals in Japan. We examined the clinical outcomes of patients who received either low-dose prasugrel (n=57) or clopidogrel (n=451) as part of triple therapy after PCI. The incidences of bleeding (TIMI major and minor) and major adverse cerebrocardiovascular events (MACCE; all-cause death, nonfatal myocardial infarction, stent thrombosis, unplanned revascularization, and stroke) were evaluated. The cumulative 1-year incidence of bleeding was not significantly different (prasugrel 5.6% vs. clopidogrel 8.1%, log-rank P=0.55). In addition, the cumulative 1-year incidence of MACCE was also not significantly different (prasugrel 11.5% vs. clopidogrel 12.3%, log-rank P=0.88).

Conclusions: Low-dose prasugrel, as part of triple therapy, did not increase the risk of bleeding compared with clopidogrel. Therefore, it can be an alternative to clopidogrel for patients with AF undergoing PCI.

Key Words: Antithrombotic therapy; Atrial fibrillation; Percutaneous coronary intervention; Prasugrel

The management of patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) remains a concern. Approximately 5–10% of patients undergoing PCI have concomitant AF and require long-term oral anticoagulation (OAC) therapy. Additionally, dual antiplatelet therapy (DAPT) consisting of aspirin and a P2Y12 receptor inhibitor is essential for preventing thrombotic adverse events, such as stent thrombosis (ST), after stent implantation. Thus, patients indicated for OAC because of AF who undergo PCI are recommended to receive triple therapy consisting of aspirin, a P2Y12 receptor inhibitor, and an OAC, if they are not at high risk for bleeding. However, triple therapy is associated with a 3- to 5-fold increase in total bleeding complications compared with other antithrombotic therapy
combinations, so the current guidelines and consensus documents recommend shortening the duration of triple therapy after PCI.

Previous studies of triple therapy have mainly focused on clopidogrel, which has been the most widely studied P2Y12 receptor inhibitor. Prasugrel is a 3rd-generation P2Y12 receptor inhibitor that rapidly and potently inhibits platelet aggregation with less pharmacological variability than clopidogrel. However, using prasugrel as part of triple therapy with aspirin and an OAC is not recommended in the current western guidelines because it is reported to increase the risk of bleeding compared with clopidogrel. In Japan, low-dose prasugrel (3.75 mg/day) was approved for use as the P2Y12 receptor inhibitor in DAPT after PCI based on a dose-finding study in Japanese patients, and its safety and efficacy in Japanese patients in cases of acute coronary syndrome (ACS) and elective PCI have been certified. However, to date the safety and efficacy of low-dose prasugrel as part of triple therapy in AF patients undergoing PCI have not been reported.

Methods

We identified 816 consecutive patients from 8 medical centers in Japan who had a history of AF or newly diagnosed AF and underwent PCI between January 1, 2011 and June 30, 2016. They were retrospectively registered in the Tokyo Women’s Medical University-Atrial Fibrillation Percutaneous Coronary Intervention registry (TWMU-AF PCI registry). Excluded were 308 patients who were prescribed non-triple therapy following PCI, and so a total of 508 patients who received triple therapy (62.3% of the identified population) following PCI were enrolled. We compared the clinical outcomes of 57 patients prescribed low-dose prasugrel and 451 patients prescribed clopidogrel as part of their triple therapy. The study flow chart is shown in Figure 1. The antithrombotic therapies and their duration were chosen at the discretion of the attending physicians after assessment of each individual’s thrombotic and bleeding risk. Anticoagulation therapy with oral warfarin was adjusted to the therapeutic range of the prothrombin time-international normalized ratio (PT-INR) recommended in the Japanese guidelines. Time in therapeutic range (TTR) was calculated by the Rosendaal method. Baseline demographic parameters of the patients were collected from the initial hospital admission records and these were used to calculate the CHADS2, CHA2DS2-VASc, and HAS-BLED scores.

Clinical Endpoints

The safety endpoint was defined as the cumulative incidence of bleeding complications defined as a composite of TIMI major and minor bleeding at 1 year. The criteria for the diagnosis of TIMI major bleeding included hemorrhagic stroke (confirmed by computed tomography or magnetic resonance imaging of the head) or clinically overt signs of hemorrhage associated with a ≥5 g/dL decrease in hemoglobin level; TIMI minor bleeding was considered to be observed blood loss and a decrease in hemoglobin level of 3–5 g/dL or a decrease in hemoglobin level ≥4 g/dL if no bleeding site was identifiable.

The efficacy endpoint was defined as the cumulative incidence of major adverse cardiac and cerebrovascular events (MACCE), a composite of all-cause death, nonfatal myocardial infarction (MI), ST, unplanned revascularization (PCI or coronary artery bypass grafting), and stroke at 1 year. MI was defined according to the definition of the European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force for the Universal Definition of Myocardial Infarction. ST was defined according to the Academic Research Consortium definition. Stroke was defined as a focal neurologic deficit lasting more than 24h, that was presumably derived from vascular events, required hospitalization or resulted in death.

Patients’ clinical information during the observation period was obtained from outpatient clinic visits or medical records review.

Statistical Analysis

Categorical variables were compared using the $\chi^2$ test. Continuous variables are expressed as mean value±standard deviation and were compared using Student’s t-test or the Mann-Whitney U-test based on the distributions. Two-sided P-values <0.05 were considered statistically significant. The cumulative incidence rate was analyzed based on the time to the first adverse event, estimated using the Kaplan-Meier method with the log-rank test.
Table 1. Patients Characteristics

| Variable                                | Prasugrel (n=57) | Clopidogrel (n=451) | P value |
|-----------------------------------------|------------------|---------------------|---------|
| Age, years                              | 72±9             | 73±8                | 0.39    |
| Male                                    | 48 (84)          | 364 (81)            | 0.60    |
| Body mass index, kg/m²                  | 23.8±5.8         | 23.5±3.7            | 0.60    |
| Paroxysmal AF                           | 33 (59)          | 223 (50)            | 0.21    |
| Hypertension                            | 42 (75)          | 352 (79)            | 0.53    |
| Diabetes                                | 29 (52)          | 195 (41)            | 0.14    |
| Insulin treatment                       | 4 (7)            | 47 (10)             | 0.44    |
| Dyslipidemia                            | 39 (68)          | 256 (57)            | 0.12    |
| Current smoker                          | 5 (9)            | 99 (22)             | 0.01    |
| CKD (eGFR <60 mL/min/1.73 m²)           | 24 (42)          | 202 (45)            | 0.64    |
| Hemodialysis                            | 9 (16)           | 44 (10)             | 0.20    |
| Heart failure                           | 13 (24)          | 137 (30)            | 0.30    |
| Peripheral artery disease               | 8 (14)           | 59 (13)             | 0.85    |
| Prior MI                                | 10 (18)          | 84 (19)             | 0.80    |
| Prior PCI                               | 18 (32)          | 140 (31)            | 0.89    |
| Prior CABG                              | 4 (7)            | 29 (6)              | 0.79    |
| Prior stroke                            | 9 (16)           | 95 (21)             | 0.37    |
| Prior major bleeding                    | 1 (2)            | 17 (4)              | 0.43    |
| Risk stratification parameter           |                  |                     |         |
| CHADS score ≥2                          | 42 (74)          | 348 (78)            | 0.50    |
| CHADS score                             | 2.2±1.3          | 2.4±1.3             | 0.21    |
| CHA2DS2-VASc score                      | 4.2±1.5          | 4.5±1.5             | 0.12    |
| HAS-BLED score                          | 2.2±0.7          | 2.3±0.7             | 0.24    |
| Medications at discharge                |                  |                     |         |
| ACEI/ARB                                | 35 (61)          | 320 (72)            | 0.11    |
| β-blocker                               | 36 (64)          | 296 (66)            | 0.81    |
| Statin                                  | 32 (57)          | 266 (60)            | 0.68    |
| Proton pump inhibitor                   | 42 (75)          | 311 (70)            | 0.49    |
| Aspirin                                 | 57 (100)         | 451 (100)           | 1.00    |
| Warfarin                                | 37 (65)          | 357 (79)            | 0.02    |
| DOAC                                    | 20 (35)          | 94 (21)             | 0.02    |
| Lesion and procedural characteristics   |                  |                     |         |
| ACS                                     | 22 (39)          | 140 (31)            | 0.24    |
| Multivessel disease                     | 17 (30)          | 161 (36)            | 0.36    |
| Femoral approach                        | 31 (54)          | 195 (43)            | 0.11    |
| DES implantation                        | 48 (81)          | 325 (73)            | 0.18    |

Data are mean±SD or n (%). ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; DES, drug eluting stent; DOAC, direct oral antiocoagulant; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention.

analyses were performed using statistical software (JMPPro 13, SAS Institute Inc., Cary, NC, USA) by an independent physician.

The study protocol was based on the regulations of the ethics committee at each collaborating hospital. All participating patients provided written informed consent. Patient enrollment was conducted according to the principles of the Declaration of Helsinki.

Results

The baseline clinical characteristics of the prasugrel and clopidogrel groups are summarized in Table 1. Mean age was 73 years, approximately 80% were male, and over 70% were at high risk for stroke (CHADS2 score ≥2). Most of the parameters were not significantly different except for the frequency of current smokers and the type of OAC.

Direct oral anticoagulant (DOAC) use was higher in the prasugrel group than in the clopidogrel group (35% vs. 21%, respectively, P=0.02). Among 394 patients who were prescribed warfarin, TTR data were available for 335 (85.0%). The overall average TTR was 52.8% and it was not significantly different between the prasugrel and clopidogrel groups (P=0.15). The mean duration of triple therapy was 230±132 days in the prasugrel group and 252±128 days in the clopidogrel group, which was not significantly different (P=0.25).

Clinical Outcomes

The Kaplan-Meier curve in Figure 2 shows the 1-year clinical outcomes after PCI. The cumulative incidence of TIMI major and minor bleeding was not significantly different.
The primary finding in the present study was that the incidences of bleeding and MACCE were not significantly different between Japanese patients with AF undergoing PCI who were prescribed prasugrel or clopidogrel as part of their triple therapy. To the best of our knowledge, this is the first report on the safety and efficacy of low-dose prasugrel as part of triple therapy compared with clopidogrel.

Discussion

The primary finding in the present study was that the incidences of bleeding and MACCE were not significantly different between Japanese patients with AF undergoing PCI who were prescribed prasugrel or clopidogrel as part of their triple therapy. To the best of our knowledge, this is the first report on the safety and efficacy of low-dose prasugrel as part of triple therapy compared with clopidogrel.

Table 2. Adverse Events at 1 Year

| Variable                  | Prasugrel (n=57) | Clopidogrel (n=451) | Log-rank P value |
|---------------------------|------------------|---------------------|------------------|
| Bleeding (TIMI major+minor) | 5.6%             | 8.1%                | 0.55             |
| TIMI major                | 1.9%             | 3.8%                | 0.49             |
| TIMI minor                | 3.7%             | 4.2%                | 0.87             |
| MACCE                     | 11.5%            | 12.3%               | 0.88             |
| All-cause death           | 3.8%             | 5.2%                | 0.65             |
| Nonfatal myocardial infarction | 0%            | 1.2%                | 0.43             |
| Stent thrombosis          | 0%               | 0.2%                | 0.73             |
| Unplanned revascularization | 2.1%            | 7.1%                | 0.17             |
| Stroke                    | 5.8%             | 3.0%                | 0.26             |
| Hemorrhagic               | 0%               | 1.4%                | 0.38             |
| Ischemic                  | 5.8%             | 2.1%                | 0.06             |

All data are event rates at 1 year estimated by Kaplan-Meier analysis.

Table 3. Sites of Bleeding

| Variable     | Prasugrel (n=57) | Clopidogrel (n=451) | P value |
|--------------|------------------|---------------------|---------|
| Intracranial | 0 (0)            | 6 (1.3)             | –       |
| Gastrointestinal | 0 (0)            | 11 (2.4)            | –       |
| Respiratory  | 0 (0)            | 1 (0.2)             | –       |
| Nose         | 1 (1.8)          | 1 (0.2)             | 0.08    |
| Urogenital   | 0 (0)            | 3 (0.6)             | –       |
| Intramuscular | 1 (1.8)          | 0 (0)               | –       |
| Access site  | 1 (1.8)          | 8 (1.8)             | 0.99    |

Data are n (%).

P=0.88; HR: 0.93, 95% CI: 0.36–2.01. The details of bleeding events and MACCE are shown in Table 2. The incidences of major and minor bleeding were also not significantly different between the groups. In terms of the components of MACCE at 1 year, all-cause death (3.8% vs. 5.2%), nonfatal MI (0% vs. 1.2%), ST (0% vs. 0.2%), unplanned revascularization (2.1% vs. 7.1%) and stroke (5.8% vs. 3.0%) were also not significantly different. Only 1 case of ST occurred on day 7 in the clopidogrel group. The sites of the bleeding events are shown in Table 3.
grel in patients with AF undergoing PCI.

In the current western guidelines, clopidogrel is the standard drug used in triple therapy with aspirin and an OAC. Prasugrel is not recommended in the current guidelines because it carries an increased risk of bleeding compared with clopidogrel. Saraff et al reported that prasugrel increased the risk of bleeding compared with clopidogrel when prescribed as part of triple therapy. However, their study had a relatively small number of patients (prasugrel n=21, clopidogrel n=336) and the dose of prasugrel was about 3-fold greater than the dose used in our study.

It has been reported that platelet inhibition by clopidogrel is attenuated in the patients who are poor metabolizers of CYP2C19, and approximately 20% of Japanese patients are poor metabolizers of CYP2C19. Also, there are still some concerns about resistance of clopidogrel, especially in Japanese patients. In contrast, the antithrombotic effect of prasugrel is not attenuated by the CYP2C19 pathway, so pharmacological interpatient variability is less than with clopidogrel. Based on the results of our study, low-dose prasugrel might be a good candidate for use as part of triple therapy.

In our study, the proportions of the types of OACs differed; the prasugrel group had a high DOAC prescription rate. However, the incidences of bleeding and MACCE were not significantly different even after evaluating the types of OACs separately (Supplementary Figures 1.2).

Recent randomized controlled studies have revealed that dual antithrombotic therapy consisting of a P2Y12 receptor inhibitor and anticoagulation therapy with a DOAC reduced the risk of bleeding vs. triple therapy without increasing thromboembolic events. According to those studies, the number of cases of dual therapy is increasing, especially for patients with a high bleeding risk. However, the guidelines do not mention the use of prasugrel as a component of dual therapy because the studies were conducted with clopidogrel as the P2Y12 receptor inhibitor.

Based on the results of our study, low-dose prasugrel might qualify as part of not only triple therapy but also dual therapy consisting of prasugrel plus a DOAC.

In terms of the component adverse events, the incidence of ischemic stroke was slightly higher in the prasugrel group (Table 2). One case of ischemic stroke in the prasugrel group occurred with off-label underdosing of the DOAC. Although it was difficult to demonstrate the influence of off-label underdosing of DOACs in our study, Steinberg et al reported that off-label dosing of DOAC was associated with increased risk for adverse events. Further studies are warranted to evaluate the optimal dose of DOACs when combined with antiplatelet drugs.

**Study Limitations**

There are several important limitations to this study. First, it was a retrospective analysis of an observational cohort, not a prospective randomized trial. Second, the number of patients was small, although we collected consecutive patients across 6 years from 8 medical centers. Third, this study included only Japanese patients. Fourth, there might have been changes in the antithrombotic regimens during the follow-up period, which we could not follow completely.

**Conclusions**

Our study suggested that low-dose prasugrel might be an alternative to clopidogrel as a part of triple therapy for patients with AF undergoing PCI. With regard to poor metabolizers of CYP2C19, further large-scale studies are warranted to determine the potential benefit of this treatment approach.

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