Prasugrel for Japanese Patients With Ischemic Heart Disease in Long-Term Clinical Practice (PRASFIT-Practice II) — 1-Year Follow-up Results of a Postmarketing Observational Study —

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Background: Although the effectiveness and safety of prasugrel for the prevention of cardiovascular events in patients with ischemic heart disease (IHD) undergoing percutaneous coronary intervention (PCI) have been demonstrated, long-term real-world data of Japanese unique doses are insufficient. Therefore, we report the results of an analysis of 1-year follow-up data from a postmarketing observational study (PRASFIT-Practice II).

Methods and Results: The safety and effectiveness analysis sets included 4,155 IHD patients receiving prasugrel (loading dose/maintenance dose, 20/3.75 mg) as dual antiplatelet therapy (DAPT) with aspirin. At 360 days (after treatment start), 62.2% continued DAPT. Cumulative incidences of major adverse cardiovascular events and stent thrombosis were 1.6% and 0.2%, respectively. Cumulative incidences of Thrombolysis In Myocardial Infarction (TIMI) major bleeding and TIMI major or minor bleeding were 1.0% and 2.0%, respectively. Risk factors for TIMI major or minor bleeding in the first 30 days of treatment were age ≥ 80 years, anemia, female sex, and liver disease, and from day 31 to the end of month 12, hypertension and peptic ulcer.

Conclusions: The 1-year follow-up results showed long-term effectiveness and safety of prasugrel at dosages approved in Japan for the treatment of IHD patients undergoing PCI.

Key Words: Bleeding adverse events; Ischemic heart disease; Major adverse cardiovascular events; Percutaneous coronary intervention; Prasugrel

Prasugrel is an adenosine diphosphate P2Y₁₂ receptor inhibitor developed in Japan and approved for the indication of prevention of cardiovascular events in patients with ischemic heart disease (IHD) undergoing percutaneous coronary intervention (PCI). As of 2019, prasugrel has been approved and is now available in more than 80 countries.

Prasugrel (initial loading dose [LD]/maintenance dose [MD], 60/10 mg) has been shown by the results of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction (TRITON-TIMI) 38, a multinational phase III trial conducted in Europe and the USA, to reduce the incidence of ischemic cardiovascular events in patients with acute coronary syndrome (ACS), as compared with clopidogrel (LD/MD, 300/75 mg); however, the inci-

dence of major bleeding adverse events (AEs) was higher in patients receiving prasugrel than in those receiving clopidogrel.¹ Therefore, to minimize bleeding risk, doses lower than those approved in Western countries were chosen (LD/MD, 20/3.75 mg) for phase III studies in Japan (PRASFIT-ACS² and PRASFIT-Elective³). The results of these studies confirmed the effectiveness and safety of prasugrel in Japanese patients. Nevertheless, in both studies, the follow-up period for the primary effectiveness endpoint was 24 weeks. In addition, in the postmarketing observational PRASFIT-Practice I study in patients with ACS,⁴ the mean observation period was limited to 65 days. Consequently, there are no data from long-term studies enrolling patients with various risk factors under real-world clinical setting.

Therefore, we carried out PRASFIT-Practice II, a large-

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Table 1. Baseline Patients' Characteristics

Characteristic	Total, n (%) (N=4,155)
Sex	
Male	3,179 (76.5)
Age (years)	
≥75	1,292 (31.1)
≥80	659 (15.9)
Mean ± SD	68.2 ± 11.2
Median (range)	69.0 (24–95)
Body weight (kg)	
≤50	561 (13.5)
Mean ± SD	63.9 ± 13.0
Medical history and complications	
Prior MI	366 (8.8)
Prior ischemic stroke	215 (5.2)
Prior PCI	596 (14.3)
Prior CABG	73 (1.8)
Peripheral arterial disease	288 (6.9)
Renal disease	383 (9.2)
On dialysis	98 (2.4)
Risk factors	
Hypertension	2,993 (72.0)
Dyslipidemia	2,841 (68.4)
Diabetes mellitus	1,635 (39.4)
Current smoker	1,105 (26.6)
Diagnosis	
ST-segment elevation MI	1,333 (32.1)
Non-ST-segment elevation MI	311 (7.5)
Unstable angina pectoris	730 (17.6)
Stable angina pectoris	1,530 (36.8)
Old MI	159 (3.8)
Other	92 (2.2)
Antithrombotic agents	
Prasugrel+aspirin	3,869 (93.1)
Prasugrel+aspirin+warfarin	75 (1.8)
Prasugrel+aspirin+DOAC	97 (2.3)
Prasugrel+NSAIDs (without aspirin)	71 (1.7)
Concomitant drugs	
Proton pump inhibitor	2,058 (49.5)
Stent type	
Drug-eluting stent	3,871 (93.2)
Puncture site	
Brachial artery	183 (4.4)
Radial artery	2,809 (67.6)
Femoral artery	1,155 (27.8)

CABG, coronary artery bypass grafting; DOAC, direct oral anticoagulants; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; PCI, percutaneous coronary intervention; SD, standard deviation.

scale postmarketing observational study with a follow-up period of 2 years, to investigate the long-term effectiveness and safety of prasugrel in Japanese patients. PRASFIT-Practice II is expected to produce useful findings to help inform clinical practice regarding the treatment of Japanese patients undergoing PCI, particularly those at high risk.

Previously, we reported the results of an analysis of the 3-month data from PRASFIT-Practice II, which showed

prasugrel to be effective and with a good safety profile based on the incidence of acute cardiovascular events and bleeding AEs during the PCI perioperative period, respectively.⁵ Here, we report the results of an analysis of the 1-year data on the effectiveness and safety of prasugrel, as well as the factors associated with the discontinuation of dual antiplatelet therapy (DAPT).

Methods

Study Design and Patients

This was a prospective postmarketing observational study of patients with IHD receiving prasugrel (clinical trial registration no. UMIN000018003). The study was conducted in accordance with Good Postmarketing Study Practice (Ministry of Health, Labour and Welfare Ordinance No. 171, December 20, 2004). The study period was between June 1, 2015 and May 31, 2018. The observation period was scheduled to be at least 2 years after the start of prasugrel treatment, regardless of treatment completion or discontinuation.

Patients with IHD who had not received treatment with prasugrel and were scheduled to undergo PCI within 30 days of starting prasugrel treatment were enrolled. Details of the eligibility criteria have been reported previously.⁵

Dosage and Administration

Prasugrel was prescribed at the attending physicians' discretion and given in accordance with the instructions in the Japanese package insert: for adults, oral administration once at an LD of 20 mg on the first day of treatment, followed by oral administration once daily at an MD of 3.75 mg. Prasugrel should be administered as DAPT with aspirin (81–100 mg/day, after an LD ≤324 mg). Patients who started prasugrel 3.75 mg approximately 5 days before PCI did not require an LD.⁵

Study Variables

Data from all case report forms (CRFs) collected at 3 months and 12 months were used for the present analysis. Study variables at 3 months included baseline patient characteristics, prasugrel administration status, use of concomitant drugs, initial coronary angiography findings, details of initial PCI, clinical laboratory data, and incidences of cardiovascular events and AEs.⁵ Study variables at 12 months were the proportion of patients continuing to receive prasugrel, use of concomitant drugs, clinical laboratory data, and incidences of cardiovascular events and AEs including bleeding.

Effectiveness and Safety

Cardiovascular events and bleeding AEs were classified according to criteria reported previously.⁴ Major adverse cardiovascular events (MACE) were defined as cardiovascular death, non-fatal myocardial infarction (MI), non-fatal ischemic stroke, and stent thrombosis. All cardiovascular events were assessed by an independent event-monitoring committee and the incidence of MACE was aggregated. Additionally, risk factors for MACE were investigated.

Data on bleeding AEs unrelated to coronary artery bypass grafting (CABG) were collected at 12 months and categorized as follows: Thrombolysis In Myocardial Infarction (TIMI) major bleeding, TIMI minor bleeding, clinically relevant bleeding, and other bleeding. Additionally, risk factors for the occurrence of TIMI major or minor

Figure 1. Continuation of DAPT (prasugrel plus aspirin) over time, and reasons for discontinuation. *Selection of multiple options was allowed. DAPT, dual antiplatelet therapy.

bleeding were investigated. AEs and adverse drug reactions (ADRs) were coded using MedDRA/J version 21.1.

Statistical Analysis

For categorical variables, the number (%) was calculated. For continuous variables, summary statistics (mean, standard deviation) were calculated. The on-treatment analysis period and the intention-to-treat (ITT) analysis period were respectively set as the period between the start and completion of prasugrel treatment, and that between the start of prasugrel treatment and the last date of the 12-month observation when each patient's CRF was collected. DAPT was defined as taking prasugrel and aspirin at the same time.

The Kaplan-Meier method was applied to estimate the adherence to DAPT by patients who received DAPT after the start of prasugrel administration. Associations between each factor and the discontinuation of DAPT were assessed using the χ^2 test. The cumulative incidence of MACE and bleeding AEs in the on-treatment population during treatment were also estimated by the Kaplan-Meier method. A multivariate Cox proportional hazards model was applied for identifying risk factors of cardiovascular events and non-CABG-related bleeding AEs. Variables in the multivariable model were selected using the stepwise selection method (a significance level of 0.10 was set to allow the addition or removal of a variable from the model). For TIMI major or minor bleeding, a multivariate Cox proportional hazards model dividing the treatment periods between within 30 days and 31 days to 12 months was applied.

For statistical analysis, we used SAS software, version 9.2 (SAS Institute Inc., Cary, NC, USA). Unless otherwise stated, statistical significance was set as an α level <0.05 in two-sided tests.

Results

Study Population

CRFs were collected from 4,270 patients. After excluding data from patients with breaches of contract, protocol deviations, or withdrawal of consent to participate in the study, data from 4,155 patients were included in both the safety analysis set and the effectiveness analysis set (**Supplementary Figure**). All 4,155 patients were included in the ITT population, in which the median observation period was 382.0 days (1st quartile, 359.0 days; 3rd quartile, 428.0 days). The median on-treatment period was 366 days (1st quartile, 272 days; 3rd quartile, 398 days).

Baseline patient characteristics are summarized in **Table 1**. Males accounted for 76.5% of patients (n=3,179). Median age was 69.0 years. Patients aged ≥ 80 years accounted for 15.9% of patients (n=659), and those with body weight ≤ 50 kg, 13.5% (n=561). Regarding diagnoses, 32.1% of patients (n=1,333) had ST-elevation MI, 7.5% (n=311) had non-ST-elevation MI, and 36.8% (n=1,530) had stable angina pectoris. In most patients (67.6%, n=2,809), PCI was conducted via the transradial approach. In the initial PCI technique, a drug-eluting stent (DES) was used in the majority of patients (93.2%, n=3,871); a biodegradable polymer DES was used in 1,572 patients. The remaining patients received a bare metal stent (BMS) (3.3%, n=139), DES+BMS (0.0%, n=2), or no stent implantation (3.4%, n=143).

Continuation of DAPT

At the time of CRF collection at 12 months, the cumulative percentage of patients continuing to receive DAPT was 62.2% at 360 days after the start of treatment (**Figure 1**). The most common reason for discontinuing treatment with prasugrel was "Completed as scheduled (treatment plan)" (61.6%, 1,126/1,827). Onset of cardiovascular events

Table 2. Factors Associated With Discontinuation of DAPT

Factor*	Total (N=4,123)	Duration of DAPT (days)		P value†
		≤360 (median, 250) (N=1,958)	>360 (median, 392) (N=2,165)	
Sex				
Male	3,154	1,455 (46.1)	1,699 (53.9)	0.0016
Female	969	503 (51.9)	466 (48.1)	
Age (years)				
<80	3,473	1,601 (46.1)	1,872 (53.9)	<0.0001
≥80	650	357 (54.9)	293 (45.1)	
Prior revascularization				
No	3,425	1,602 (46.8)	1,823 (53.2)	0.0160
Yes	645	335 (51.9)	310 (48.1)	
Prior CABG				
No	4,052	1,915 (47.3)	2,137 (52.7)	0.0261
Yes	71	43 (60.6)	28 (39.4)	
Prior MI				
No	3,725	1,754 (47.1)	1,971 (52.9)	0.0390
Yes	360	190 (52.8)	170 (47.2)	
Concomitant drugs‡				
No	3,951	1,840 (46.6)	2,111 (53.4)	<0.0001
Yes	172	118 (68.6)	54 (31.4)	
CCr (mL/min)				
Normal (>80)	1,359	582 (42.8)	777 (57.2)	0.0002
Mild (>50, ≤80)	1,412	690 (48.9)	722 (51.1)	
Moderate (≥30, ≤50)	552	288 (52.2)	264 (47.8)	
Severe (<30)	174	93 (53.4)	81 (46.6)	
CREDO-Kyoto thrombotic risk score⁶				
Low (0–1 point)	2,061	913 (44.3)	1,148 (55.7)	<0.0001
Intermediate (2–3 points)	1,115	565 (50.7)	550 (49.3)	
High (≥4 points)	402	220 (54.7)	182 (45.3)	
CREDO-Kyoto bleeding risk score⁶				
Low (0 points)	2,216	998 (45.0)	1,218 (55.0)	<0.0001
Intermediate (1–2 points)	977	484 (49.5)	493 (50.5)	
High (≥3 points)	303	174 (57.4)	129 (42.6)	

Number of patients (%) is shown. *Only factors with $P < 0.05$ are included. †Calculated using the χ^2 test.

‡Aspirin+warfarin, or DOAC. CCr, creatinine clearance; CREDO-Kyoto, Coronary Revascularization Demonstrating Outcome Study in Kyoto; DAPT, dual antiplatelet therapy. Other abbreviations as in Table 1.

or AEs was the reason for 10.8% of discontinuations of treatment with prasugrel (197/1,827).

Analyses of factors associated with DAPT discontinuation, stratified by duration of DAPT (i.e., ≤360 days and >360 days), showed that female sex, age ≥80 years, prior revascularization, prior CABG, prior MI, concomitant drug use (aspirin+warfarin, or direct oral anticoagulants), low creatinine clearance (CCr) value, Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) high thrombotic risk score,⁶ and CREDO-Kyoto high bleeding risk score⁶ were factors affecting DAPT duration less than 360 days (Table 2). **Supplementary Table 1** shows the types of antiplatelet drugs after the start of DAPT with prasugrel and aspirin. The majority of patients received aspirin as single antiplatelet therapy after the completion or discontinuation of prasugrel.

Effectiveness

The cumulative incidence of MACE at 360 days after the start of prasugrel treatment was 1.6%; the most common MACE was cardiovascular death (0.7%) (Figure 2A). The

cumulative incidence of stent thrombosis was 0.2% (Figure 2A). The Cox proportional hazards model identified CCr <30 mL/min, prior MI, prior ischemic stroke, and anemia as risk factors for MACE (Table 3).

Safety

The cumulative incidences of TIMI major bleeding, TIMI major or minor bleeding, and all bleeding at 360 days after the start of prasugrel treatment were 1.0%, 2.0%, and 5.5%, respectively (Figure 2B). Incidences of bleeding AEs in the on-treatment and ITT populations by bleeding type are shown in **Supplementary Table 2**. The Cox proportional hazards model identified age ≥80 years, anemia, and peptic ulcer as risk factors for TIMI major or minor bleeding (Table 3).

Kaplan-Meier curves showed a high incidence of TIMI major or minor bleeding from the onset of treatment (early treatment phase, i.e. the first 30 days of treatment, 0.5%; later treatment phase, i.e., day 31 to the end of month 12, 1.5%) (Figure 2C). Analyses of risk factors using the Cox proportional hazards model identified age ≥80 years, anemia,

Figure 2. Cumulative incidence of cardiovascular events and bleeding AEs while on prasugrel treatment. Kaplan-Meier curves for cumulative incidence of (A) cardiovascular (CV) events, (B) bleeding AEs, and (C) TIMI major or minor bleeding (treatment periods divided between within 30 days and 31 days to 12 months). *CV death, non-fatal MI, non-fatal ischemic stroke, and stent thrombosis. AE, adverse event; CI, confidence interval; MACE, major adverse cardiovascular events; MI, myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.

Table 3. Incidence of Cardiovascular Events or TIMI Major or Minor Bleeding by Cause on Treatment

Factor	Hazard ratio (95% CI)	P value
Cardiovascular events (MACE*)		
CCr (<30 mL/min)	4.18 (2.14, 8.19)	<0.0001
Prior MI	2.42 (1.25, 4.68)	0.0085
Prior ischemic stroke	2.52 (1.14, 5.55)	0.0222
Anemia	2.34 (1.08, 5.06)	0.0306
Female sex	1.64 (0.95, 2.83)	0.0761
TIMI major or minor bleeding (throughout treatment period)		
Age (≥80 years)	2.41 (1.48, 3.94)	0.0004
Anemia	2.63 (1.28, 5.41)	0.0087
Peptic ulcer	2.36 (1.06, 5.25)	0.0349
Hypertension	1.81 (0.97, 3.37)	0.0610
TIMI major or minor bleeding (treatment period, ≤30 days)		
Age (≥80 years)	7.37 (2.75, 19.70)	<0.0001
Anemia	7.51 (2.56, 22.06)	0.0002
Female sex	3.84 (1.38, 10.65)	0.0098
Liver disease	4.44 (1.41, 14.03)	0.0111
Current smoker	2.92 (0.98, 8.68)	0.0546
TIMI major or minor bleeding (treatment period, 31 days to end of 12 months)		
Hypertension	2.98 (1.27, 6.98)	0.0119
Peptic ulcer	2.82 (1.12, 7.10)	0.0272
Age (≥80 years)	1.72 (0.92, 3.21)	0.0893

*Cardiovascular death, non-fatal MI, non-fatal ischemic stroke, and stent thrombosis. CI, confidence interval; MACE, major adverse cardiovascular events; TIMI, Thrombolysis In Myocardial Infarction. Other abbreviations as in Tables 1,2.

female sex, and liver disease as risk factors for TIMI major or minor bleeding in the early treatment phase, and hypertension and peptic ulcer as risk factors in the later treatment phase (Table 3).

In the present study, 2,058 patients were receiving concomitant treatment with proton pump inhibitors (PPI). TIMI major or minor gastrointestinal bleeding occurred in 1.0% (21/2,058) and 0.8% (17/2,097) of those with and without concomitant use of PPI, respectively ($P=0.4777$). In the multivariate Cox regression analyses, concomitant use of PPI was not identified as a factor associated with bleeding.

Frequently observed ADRs other than bleeding included hepatic function abnormal (9 events), rash (8 events), diarrhea (5 events) and urticaria (3 events).

Effect of Age on Safety and Effectiveness

The incidences of bleeding AEs and cardiovascular events are shown in **Supplementary Table 3A,B**. Both incidences were higher in patients aged ≥80 years than in patients aged <80 years.

Discussion

This report presents data from a postmarketing observational study with a 1-year follow-up of 4,155 Japanese consecutive patients with IHD undergoing PCI. The median observation period was 382.0 days (1st quartile, 359.0 days; 3rd quartile, 428.0 days), and sufficient data for analysis were collected. The results of the analysis showed the effectiveness and safety of prasugrel in a real-world clinical setting.

In the present study, risk scores determined by the

CREDO-Kyoto registry cohort 2, a large-scale observational study conducted in Japan,⁶ were used to stratify patients by bleeding risk and thrombotic risk. The results showed that bleeding and thrombotic risk distributions were similar to those in the CREDO-Kyoto registry cohort 2 (Figure 3); therefore, we consider that the findings of the present analysis are generalizable to the treatment of Japanese patients in real-world clinical settings. The results are also expected to be beneficial to other Asian countries where prasugrel is used at the same doses approved in Japan.

Over 60% of the patients (cumulative percentage) continued to receive DAPT at 360 days after the start of DAPT treatment. Common factors associated with DAPT discontinuation were female sex, age ≥80 years, and renal disease; these are well known risk factors for bleeding,⁶⁻⁸ so the duration of DAPT may have been shortened during the early treatment phase because of concerns regarding the risk of bleeding. As the data used in the present analysis were limited to those collected at 12 months, we plan to conduct a more accurate analysis to identify the effect of discontinuation of DAPT on 2-year outcomes.

The findings of the present analysis are important because they show the effectiveness of prasugrel, at dosages specific to Japan, when used for a longer term than in previously reported clinical trials in Japan, namely, PRASFIT-ACS² and PRASFIT-Elective³ (12 months in this analysis vs. 24 weeks in the previous studies).

In the present analysis, the incidence of stent thrombosis was very low (0.2%) and no cases of stent thrombosis occurred from 90 days onwards (Figure 2A). These findings may be related to the immediate effect of prasugrel in preventing subacute stent thrombosis as well as improvements

Figure 3. Distribution of CREDO-Kyoto thrombotic and bleeding risk scores. Numbers of patients (%) are shown below the graph.

in the design/type of stents used and the consistent platelet inhibition achieved by prasugrel. The antiplatelet effects of prasugrel are unaffected by genetic polymorphism.^{9,10}

In the previous PRASFIT-Practice II interim analysis, multivariate analyses of risk factors for cardiovascular events were carried out for all cardiovascular events.⁵ In contrast, in the present analysis we focused on the risk of MACE, because these are considered more severe and clinically important than other cardiovascular events. The results indicated that CCr <30 mL/min, prior MI, prior ischemic stroke, and anemia were risk factors for MACE. It has been shown that risk factors for MACE often overlap with those for bleeding AEs, which are not easy to differentiate.^{6,7} The factors identified in the present study were consistent with those identified and considered important in the previous analysis, and no new risk factors were identified. Notably however, in the present study, there was little overlap in the risk factors for MACE and bleeding AEs; this is a beneficial finding for clinical practice. Regarding MACE, in addition to prior ischemia, systemic conditions such as renal disease and anemia were found to be important factors, whereas, for bleeding AEs, the factors of prior bleeding (e.g., peptic ulcer) and age should be taken into consideration. In patients with these background factors, each condition should be carefully assessed to determine an optimized therapeutic strategy.

The incidence of non-cardiovascular death was 1.0% (42/4,155) in the ITT population at 12 months (**Supplementary Table 4**). Of the 22 non-cardiovascular deaths that occurred after the discontinuation of prasugrel treatment, the main causes were cancer (9/4,155) and pneumonia (5/4,155); most were not AEs of concern caused by prasugrel.

The results of the present analysis showed a low incidence of bleeding; the incidence of non-CABG-related TIMI major or minor bleeding at 360 days was 2.0%. In consideration of treatment duration, 0.5% of non-CABG-related TIMI major or minor bleeding occurred in the first 30 days of treatment. Thus, although the present analysis included

many patients at high risk of bleeding AEs under real-world clinical setting, the incidence of bleeding AEs was lower than that reported in TRITON-TIMI 38¹ and PRASFIT-ACS,² both in terms of overall incidence and the incidence in the early treatment phase. A possible reason for this finding is that in the present analysis, after the initial PCI, only 2 patients experienced bleeding (TIMI major or minor bleeding) at the puncture site.⁵ This may be because, although the femoral artery has been chosen as the principal access site for PCI in the past, recently the radial artery is increasingly chosen, as the transradial approach is a safe alternative, leading to reductions in mortality, major bleeding complications, MACE and vascular complications compared with the femoral artery approach.¹¹

This explanation is consistent with our interpretation of the results of the previous 3-month interim analysis.⁵ However, approximately 25% of the bleeding AEs occurred during the early treatment phase. Therefore, further inhibition of bleeding AEs during this period is deemed critical for reducing the incidence of bleeding AEs during the treatment.

Regarding the results of the multivariate analyses to identify risk factors for bleeding AEs, although all bleeding AEs were included in the previous 3-month interim analysis, in the present analysis we focused on TIMI major or minor bleeding, which is more likely to be severe and clinically problematic. We found that age ≥80 years, anemia, female sex, and liver disease were risk factors for TIMI major or minor bleeding during the early treatment phase. Patients aged ≥80 years accounted for 15.9% in the present study. In addition to the fact that age ≥80 years was identified as a risk factor for bleeding in the early treatment phase, the incidences of non-fatal stroke and cardiovascular death were also high in this population. Therefore, a tailored treatment approach should be warranted for patients at high bleeding risk, and in particular, for elderly patients. Although, as previously reported, the MD of prasugrel was 3.75 mg in ≥99% of patients, the risk of bleeding may be further minimized by reducing the MD in the early

treatment phase (e.g., to 2.5mg) or by using an optimal puncture site (e.g., choosing the transradial approach). Additionally, prasugrel monotherapy could be considered in the future.

The finding that the cumulative incidences of non-CABG-related TIMI major bleeding and MACE were low (1.0% and 1.6%, respectively) and that the incidence of TIMI major bleeding was lower than that of MACE indicated that prasugrel given at dosages approved in Japan would be useful to prevent major bleeding and provides a net clinical benefit in the real-world clinical setting.

Study Limitations

The data used in this analysis were from CRFs collected for each patient at the last date of the 12-month observation period. Therefore, for some patients the observation period was slightly less than 12 months.

Another limitation is that bleeding risk factors were investigated in 2 treatment periods: the period during the first 30 days and that from day 31 to the end of month 12. The analysis for the early treatment phase included data from all patients, whereas the analysis for the later treatment phase excluded data from patients who had discontinued or experienced bleeding in the first 30 days. Therefore, caution is required in interpreting the results of the 2 analyses, because the groups of patients used in each analysis are not comparable. In addition, although the study enrolled patients consecutively, patients who could give written consent and receive long-term treatment were enrolled; thus some patients with very severe IHD may have not been enrolled and this may contribute to the low incidence of events observed.

Conclusions

The 1-year follow-up results of the PRASFIT-Practice II were consistent with the results of the previous 3-month interim analysis showing the effectiveness and safety of prasugrel at dosages approved in Japan for patients with IHD undergoing PCI.

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References

1. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; **357**: 2001–2015.
2. Saito S, Isshiki T, Kimura T, Ogawa H, Yokoi H, Nanto S, 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.
3. Isshiki T, Kimura T, Ogawa H, Yokoi H, Nanto S, Takayama M, et al. Prasugrel, a third-generation P2Y₁₂ receptor antagonist, in patients with coronary artery disease undergoing elective percutaneous coronary intervention. *Circ J* 2014; **78**: 2926–2934.
4. Nakamura M, Iizuka T, Sagawa K, Abe K, Chikada S, Arai M. Prasugrel for Japanese patients with acute coronary syndrome in short-term clinical practice (PRASFIT-Practice I): A postmarketing observational study. *Cardiovasc Interv Ther* 2018; **33**: 135–145.
5. Nakamura M, Kozuma K, Kitazono T, Iizuka T, Sekine T, Shiosakai K, et al. Prasugrel for Japanese Patients With Ischemic Heart Disease in Long-Term Clinical Practice (PRASFIT-Practice II): A 3-month interim analysis of a postmarketing observational study. *Circ J* 2019; **83**: 637–646.
6. Natsuaki M, Morimoto T, Yamaji K, Watanabe H, Yoshikawa Y, Shiomi H, et al. Prediction of thrombotic and bleeding events after percutaneous coronary intervention: CREDO-Kyoto thrombotic and bleeding risk scores. *J Am Heart Assoc* 2018; **7**: e008708.
7. Costa F, van Klaveren D, James S, Heg D, Raber L, Feres F, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: A pooled analysis of individual-patient datasets from clinical trials. *Lancet* 2017; **389**: 1025–1034.
8. Baber U, Mehran R, Giustino G, Cohen DJ, Henry TD, Sartori S, et al. Coronary thrombosis and major bleeding after Pci with drug-eluting stents: Risk scores from PARIS. *J Am Coll Cardiol* 2016; **67**: 2224–2234.
9. Brandt JT, Close SL, Iturria SJ, Payne CD, Farid NA, Ernest CS 2nd, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. *J Thromb Haemost* 2007; **5**: 2429–2436.
10. Ogawa H, Isshiki T, Kimura T, Yokoi H, Nanto S, Takayama M, et al. Effects of CYP2C19 allelic variants on inhibition of platelet aggregation and major adverse cardiovascular events in Japanese patients with acute coronary syndrome: The PRASFIT-ACS study. *J Cardiol* 2016; **68**: 29–36.
11. Nardin M, Verdoia M, Barbieri L, Schaffer A, Suryapranata H, De Luca G. Radial vs. femoral approach in acute coronary syndromes: A meta-analysis of randomized trials. *Curr Vasc Pharmacol* 2017; **16**: 79–92.

Supplementary Files

Please find supplementary file(s);
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