Efficacy and Safety of Adjusted-Dose Prasugrel Compared With Clopidogrel in Japanese Patients With Acute Coronary Syndrome

– The PRASFIT-ACS Study –

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Background: Prasugrel is an antiplatelet agent that shows more prompt, potent, and consistent platelet inhibition than clopidogrel. The objective of this study was to confirm the efficacy and safety of prasugrel at loading/maintenance doses of 20/3.75 mg.

Methods and Results: Japanese patients (n=1,363) with acute coronary syndrome undergoing percutaneous coronary intervention were randomized to either prasugrel (20/3.75 mg) or clopidogrel (300/75 mg), both in combination with aspirin (81–330 mg for the first dose and 81–100 mg/day thereafter), for 24–48 weeks. The primary efficacy endpoint was the incidence of major adverse cardiovascular events (MACE) at 24 weeks, defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal ischemic stroke. We compared the incidence of MACE between the 2 groups using point estimates. Safety outcomes included the incidence of bleeding events until 2 weeks after the last dose. The incidence of MACE at 24 weeks was 9.4% in the prasugrel group and 11.8% in the clopidogrel group (risk reduction 23%, hazard ratio 0.77, 95% confidence interval 0.56–1.07). The incidence of non-coronary artery bypass graft-related major bleeding was similar in both groups (1.9% vs. 2.2%).

Conclusions: Prasugrel 20/3.75 mg was associated with a low incidence of ischemic events, similar to the results of TRITON-TIMI 38, and with a low risk of clinically serious bleeding in Japanese ACS patients. (*Circ J* 2014; **78**: 1684–1692)

Key Words: Acute coronary syndrome; Clopidogrel; Major adverse cardiovascular events; Percutaneous coronary intervention; Prasugrel

The incidence of coronary artery disease is steadily increasing in Japan, and is accompanied by an increase in the number of percutaneous coronary interventions (PCI).¹ Patients undergoing PCI are usually started on dual antiplatelet therapy, consisting of aspirin and a thienopyridine,

to prevent recurrent ischemia and stent thrombosis.^{2,3} Although clopidogrel is often used with aspirin, the responses to clopidogrel vary in Asian patients.⁴

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Prasugrel is a new-generation thienopyridine antiplatelet agent that provides more prompt, potent and consistent platelet inhibition than clopidogrel.⁵ The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) in patients with acute coronary syndrome (ACS) undergoing PCI demonstrated that prasugrel resulted in significantly fewer ischemic events but had a higher incidence of bleeding compared with clopidogrel.⁶ Based on analyses of prespecified clinical features in TRITON-TIMI 38, age ≥ 75 years, body weight < 60 kg, and history of stroke or transient ischemic attack (TIA) were identified as risk factors for bleeding.

The Japanese package insert for clopidogrel includes precautions for careful administration in patients with a low body weight and in elderly patients because the risk of bleeding might be increased. Recent reports have also noted that other antithrombotic agents increased the bleeding risk in Japanese patients.⁷ Considering the higher average age and lower body weight of Japanese patients compared with Western patients, we considered that lower doses of prasugrel could diminish the risk of bleeding during dual antiplatelet therapy in Japanese patients. A recent Japanese Phase II trial (unpublished data) showed that administration of prasugrel (loading dose (LD)/maintenance dose (MD): 20/3.75 mg for 12 weeks) was associated with a similar incidence of bleeding events compared with a standard clopidogrel regimen (LD/MD: 300/75 mg), independent of the age and body weight of patients.

The objective of the PRASFIT-ACS (PRASugrel compared with clopidogrel For Japanese patients with ACS undergoing PCI) study was to confirm the effects of a prasugrel dosing regimen adjusted for Japanese patients (LD/MD: 20/3.75 mg) on the incidence of major adverse cardiovascular events (MACE) and bleeding events, compared with the standard clopidogrel dosing regimen approved in Japan (LD/MD: 300/75 mg) as a control group, in ACS patients undergoing PCI.

Methods

Study Design

This randomized, double-blind, double-dummy, parallel-group study was conducted at 162 centers in Japan between December 2010 and June 2012. The database was locked in September 2012. The study consisted of a 24–48-week treatment period and a 14-day follow-up period.

Patients

The present study was conducted in Japanese ACS patients who satisfied all of the following criteria and were scheduled for coronary artery stenting: males/females aged ≥ 20 years; presence of chest discomfort or ischemic symptoms lasting ≥ 10 min within 72 h before randomization; ST-segment deviation ≥ 1 mm, or T-wave inversion ≥ 3 mm, or elevated levels of cardiac biomarkers for necrosis.

The major exclusion criteria were: refractory life-threatening ventricular arrhythmia; history or a current diagnosis of thrombocytopenia purpura or agranulocytosis; pancytopenia or aplastic anemia; history of intracranial bleeding; history of ischemic stroke/TIA; history of or predisposition to hemorrhagic disease; poorly controlled hypertension; severe hepatic or renal impairment; New York Heart Association (NYHA) grade IV heart failure; and administration of a thienopyridine

drug within 5 days before starting the study drug or a thrombolytic drug within 24 h before starting the study drug. All of the patients provided informed consent before enrollment.

The present study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice,^{8,9} and was approved by the institutional review boards at all 162 participating centers.

Treatments

Eligible patients were randomized to either prasugrel or clopidogrel in a 1:1 ratio after they provided written informed consent. Randomization was performed using a uniform random numbers list generated using SAS software (SAS Institute, Cary, NC, USA).

The LD of prasugrel (20 mg) or clopidogrel (300 mg) was to be administered before PCI, except in urgent cases, when it could be administered up to 1 h after leaving the cardiac catheter laboratory. In most cases, PCI was performed immediately after obtaining informed consent, or at most several days after obtaining informed consent. The MD of prasugrel (3.75 mg) or clopidogrel (75 mg) was administered once daily after breakfast, starting on the day after the LD, and was continued for the remainder of the treatment period. Aspirin (81–330 mg for the first dose and 81–100 mg/day thereafter) was concomitantly administered during the treatment period. The use of other antiplatelet drugs, anticoagulant drugs, thrombolytic drugs, or continuous administration of oral acidic non-steroidal anti-inflammatory drugs was prohibited.

Clinic visits were scheduled every 2–4 weeks for the first 12 weeks, and every 12 weeks thereafter. Although 48 weeks was the recommended duration of drug administration, the investigators could complete drug administration at week 24 if deemed appropriate for the individual patient, taking into account stent type and the recommended duration of thienopyridine administration, as stated in the package inserts for the stents.

Efficacy

Patients who were administered at least one dose of the study drugs were followed up for 24–48 weeks to evaluate efficacy events. The primary efficacy endpoint was the incidence of MACE at 24 weeks, which was defined as a composite of cardiovascular death, nonfatal myocardial infarction (MI), and nonfatal ischemic stroke.

Cardiovascular death was defined as any death attributable to a cardiovascular event. Stroke was defined as the presence of neurological symptoms or signs consistent with stroke and confirmation by magnetic resonance imaging. Stroke was classified as ischemic (cerebral infarction) or non-ischemic stroke. Nonfatal MI was defined as events fulfilling at least one of the following 3 criteria. (1) In patients with normal creatine kinase (CK)-MB before PCI/coronary artery bypass grafting (CABG), CK-MB had to be (a) ≥ 3 -fold the upper limit of normal (ULN) in 2 samples obtained, or ≥ 5 -fold the ULN in 1 sample obtained < 48 h after PCI, or (b) ≥ 10 -fold the ULN in 1 sample obtained < 48 h after CABG. Patients whose CK-MB exceeded the ULN before PCI/CABG had to show a transient decrease with a subsequent increase of ≥ 1.5 -fold the previous value and satisfy (a) or (b). (2) More than 48 h after PCI, the CK-MB or troponin levels had to be ≥ 2 -fold the ULN, accompanied by 1 or more of the following: new or recurrent sustained ischemic chest pain, hemodynamic decompensation, or new or recurrent ST elevation/depression ≥ 0.1 mV. (3) Abnormal Q waves had to persist for ≥ 0.04 s.

As a secondary endpoint, we analyzed the incidence of the primary endpoint from randomization to completion of the

follow-up period.

The other efficacy endpoints were the incidence of all-cause death, myocardial ischemia requiring rehospitalization, revascularization, and stent thrombosis (defined as definite or probable according to the Academic Research Consortium).¹⁰

Safety

The safety endpoint was the incidence of non-CABG-related bleeding events that occurred up until 2 weeks after the last dose. Bleeding events were classified as follows. (1) Non-CABG-related TIMI major bleeding (major bleeding): intracranial bleeding or clinically significant bleeding accompanied by a decrease in hemoglobin ≥ 5 g/dl. (2) Non-CABG-related TIMI minor bleeding (minor bleeding): clinically significant bleeding accompanied by a decrease in hemoglobin of 3– <5 g/dl. (3) Clinically relevant non-major or minor bleeding: bleeding from critical sites (including retroperitoneal, intrapericardial, intravitreous/retinal, intraspinal, and intra-articular hemorrhage); gastrointestinal bleeding accompanied by decreased hemoglobin; gross hematuria not attributed to external factors; epistaxis requiring otolaryngology; gingival bleeding requiring dental treatment; bleeding requiring discontinuation of the study treatment at the investigator's discretion. These bleeding events were accompanied by a decrease in hemoglobin <3 g/dl. (4) Other bleeding: all bleeding other than major bleeding, minor bleeding, or clinically relevant non-major or minor bleeding events.

Life-threatening bleeding was defined as a composite of the following major bleeding events: fatal bleeding, bleeding requiring intravenous inotropic medication, and bleeding requiring transfusion of ≥ 4 units of red blood cells.

We also examined the incidence of treatment-emergent adverse events (AEs) that occurred up to 14–35 days after the last dose.

Statistical Analysis

All efficacy events were analyzed by the Efficacy Evaluation

Committee (comprising S.N., M.T. and K.K.) and bleeding events were analyzed by the Safety Evaluation Committee (comprising M. Nishikawa and S.M.); both committees were independent of the study sponsor. For events that were considered to satisfy the criteria of efficacy or bleeding events, the relevant committee re-evaluated and classified the events in a blinded manner. At the time of planning this study, we determined that it was not possible to enroll a sufficient number of Japanese patients to detect non-inferiority or superiority for the incidence of MACE between prasugrel and clopidogrel. However, prasugrel achieved a significant reduction in the incidence of MACE compared with clopidogrel in ACS patients in TRITON-TIMI 38. For these reasons, we determined whether the incidence of MACE was lower in the prasugrel group than in the clopidogrel group by determining point estimates, and ensuring that the hazard ratio (HR) was <1.0 . Assuming that the incidence of MACE was 15% lower in the prasugrel group than in the clopidogrel group,⁶ 600 patients were required per group. This would provide an estimated HR <1.0 at a probability >0.8 .

Efficacy analyses were performed using the full analysis set, which consisted of all patients who took at least one dose of study drugs, did not have a serious violation of the study protocol, and who had data collected after starting administration of the study drug. Safety analyses were done in all patients who received at least one dose of the study drug and who did not have a serious violation of the study protocol.

HRs for the prasugrel group relative to the clopidogrel group, with 2-sided 95% confidence intervals (CI), were calculated for the primary efficacy endpoint and for other endpoints using the Cox proportional hazard model with adjustment for age (<75 vs. ≥ 75 years) and number of lesions treated during PCI (no PCI, 1 lesion, multiple lesions). The incidence of events in each group was estimated using the Kaplan-Meier method. All analyses were performed using SAS version 9.2 (SAS Institute).

Table 1. Clinical Characteristics of Japanese Patients With ACS Undergoing PCI

	Prasugrel (n=685)	Clopidogrel (n=678)	All patients (n=1,363)
	n (%)	n (%)	n (%)
Female	149 (21.8)	140 (20.6)	289 (21.2)
Age, years			
Mean $\pm$ SD	65.4 $\pm$ 11.4	65.1 $\pm$ 11.3	65.2 $\pm$ 11.4
Median (range)	65 (32–95)	66 (32–93)	66 (32–95)
≥ 75 years	165 (24.1)	148 (21.8)	313 (23.0)
Body weight, kg	64.2 $\pm$ 12.3	64.4 $\pm$ 11.2	64.3 $\pm$ 11.8
≤ 50	85 (12.4)	72 (10.6)	157 (11.5)
≤ 60	266 (38.9)	240 (35.4)	506 (37.2)
Body mass index	24.2 $\pm$ 3.6	24.2 $\pm$ 3.3	24.2 $\pm$ 3.4
Current smoker	273 (39.9)	279 (41.2)	552 (40.5)
ACS type			
UA/NSTEMI	343 (50.1)	337 (49.7)	680 (49.9)
UA	156 (22.8)	124 (18.3)	280 (20.5)
NSTEMI	187 (27.3)	213 (31.4)	400 (29.3)
STEMI	340 (49.6)	341 (50.3)	681 (50.0)
No. of treated lesion sites (first PCI)			
1	470 (68.6)	455 (67.1)	925 (67.9)
>1	181 (26.4)	182 (26.8)	363 (26.6)
No first PCI	34 (5.0)	41 (6.0)	75 (5.5)
Hypertension	495 (72.3)	491 (72.4)	986 (72.3)
Dyslipidemia	516 (75.3)	500 (73.7)	1,016 (74.5)
Diabetes mellitus	250 (36.5)	237 (35.0)	487 (35.7)
Prior MI	34 (5.0)	35 (5.2)	69 (5.1)
Prior revascularizations	40 (5.8)	45 (6.6)	85 (6.2)
Prior CABG	6 (0.9)	4 (0.6)	10 (0.7)
Prior TLR	15 (2.2)	13 (1.9)	28 (2.1)
CrCl (ml/min)	n=622	n=625	n=1,247
>60	486 (78.1)	507 (81.1)	993 (79.6)
≤ 60	136 (21.9)	118 (18.9)	254 (20.4)
Concomitant therapy			
Proton-pump inhibitor	282 (41.2)	287 (42.3)	569 (41.7)
Statin	346 (50.5)	328 (48.4)	674 (49.4)
Ca-blocker	184 (26.9)	159 (23.5)	343 (25.2)
β -blocker	122 (17.8)	114 (16.8)	236 (17.3)
Stent type			
Bare metal	353 (51.5)	353 (52.1)	706 (51.8)
Drug-eluting	291 (42.5)	278 (41.0)	569 (41.7)

Values are n (%) or mean $\pm$ standard deviation.

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CrCl, creatinine clearance (estimated using the Cockcroft-Gault formula); MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TLR, target lesion revascularization; UA, unstable angina.

Results

Study Population

Of 1,465 patients who gave informed consent, 1,385 were randomized and 1,363 received either prasugrel (n=685) or clopidogrel (n=678) (**Figure 1**); 80 patients discontinued before randomization and 22 patients discontinued after randomization but before administration of the LD because of the absence of significant stenosis, unsuitability for stent implantation, or failure to meet eligibility criteria. Overall, 183 and 190 patients in the prasugrel and clopidogrel groups, respectively, discontinued after starting the study drug.

Table 1 shows the characteristics of the 1,363 patients included in the full analysis set. There were no differences be-

tween the 2 groups in terms of baseline demographic factors, medical history, concomitant therapy, and procedural variables. The mean duration of study drug administration was 213.5 days in the prasugrel group and 207.5 days in the clopidogrel group. The median dose of aspirin at the time of LD was 200mg, and that during follow-up was 100mg in both treatment groups. The mean duration of aspirin administration was 230.7 days in the prasugrel group and 224.0 days in the clopidogrel group.

Efficacy

Table 2 compares the efficacy endpoints between the prasugrel and clopidogrel groups. The primary efficacy endpoint, the incidence of MACE at 24 weeks, was 9.4% (95% CI 7.3–11.8)

Table 2. Comparison of the Efficacy Endpoints at Specific Times in Japanese Patients With ACS Undergoing PCI

Efficacy endpoint	Prasugrel (n=685)	Clopidogrel (n=678)	HR (95% CI)
	n (%) [*]	n (%) [*]	
MACE through to week 24	64 (9.4)	80 (11.8)	0.77 (0.56–1.07)
CV death	9 (1.3)	6 (0.9)	1.45 (0.51–4.07)
Nonfatal MI	52 (7.6)	68 (10.1)	0.74 (0.52–1.06)
Nonfatal ischemic stroke	3 (0.4)	7 (1.0)	0.43 (0.11–1.68)
Components of MACE through to week 24			
All-cause death	9 (1.3)	8 (1.2)	1.09 (0.42–2.83)
Nonfatal stroke	3 (0.4)	8 (1.2)	0.38 (0.10–1.43)
Revascularization	31 (4.6)	32 (4.8)	0.96 (0.58–1.57)
Stent thrombosis	3 (0.4)	5 (0.7)	0.60 (0.14–2.51)
MACE through to week 48	74 (11.1)	84 (12.7)	0.85 (0.62–1.16)
CV death	10 (1.5)	8 (1.4)	1.21 (0.48–3.06)
Nonfatal MI	58 (8.7)	68 (10.1)	0.83 (0.58–1.17)
Nonfatal ischemic stroke	6 (1.0)	9 (1.4)	0.66 (0.24–1.86)
Components of MACE through to week 48			
All-cause death	11 (1.8)	11 (2.1)	0.96 (0.42–2.22)
Nonfatal stroke	6 (1.0)	10 (1.5)	0.60 (0.22–1.64)
Revascularization	107 (20.0)	96 (19.4)	1.10 (0.84–1.45)
Stent thrombosis	4 (0.6)	5 (0.7)	0.80 (0.21–2.96)
MACE[‡] while on treatment[†]	67 (10.7)	78 (12.0)	0.83 (0.60–1.15)
CV death	4 (0.6)	5 (0.8)	0.76 (0.20–2.84)
Nonfatal MI	58 (9.3)	67 (10.2)	0.84 (0.59–1.19)
Nonfatal ischemic stroke	5 (0.9)	6 (1.1)	0.82 (0.25–2.70)
Components of MACE while on treatment[†]			
All-cause death	5 (1.1)	5 (0.8)	0.95 (0.27–3.28)
Nonfatal stroke	5 (0.9)	7 (1.2)	0.71 (0.22–2.23)
Revascularization	83 (19.5)	72 (17.2)	1.13 (0.83–1.55)
Stent thrombosis	4 (0.6)	5 (0.8)	0.79 (0.21–2.95)

^{*}Cumulative incidence. [†]From first dose of study treatment until 14 days after last treatment. [‡]Composite of cardiovascular death, nonfatal MI, and nonfatal ischemic stroke.

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiac events. Other abbreviations as in Table 1.

Figure 2. Kaplan-Meier estimates of the incidence of the primary efficacy endpoint, major coronary adverse events (MACE: composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal ischemic stroke) at 24 weeks in the PRASIT-ACS study (PRASugrel compared with clopidogrel For Japanese patients with ACS undergoing PCI). Based on full analysis set. *Risk reduction was calculated as: $(1 - \text{hazard ratio}) \times 100$.

Figure 3. Hazard ratios (HRs) and risk reduction for the primary efficacy endpoint and other efficacy events in prespecified subgroups of patients from start of drug administration to 24 weeks in the PRASFIT-ACS study (PRASugrel compared with clopidogrel For Japanese patients with ACS undergoing PCI). Based on the full analysis set. The HRs are based on Cox regression using age (≥75, <75 years) and the number of treated lesion sites (first PCI) as covariates. If a characteristic was used as a covariate, it was removed from the Cox regression model. UA, unstable angina; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; CrCl, creatinine clearance (estimated using the Cockcroft-Gault formula).

Table 3. Non-CABG-Related Bleeding Events in Japanese Patients With ACS Undergoing PCI

Bleeding event	All			Spontaneous		
	Prasugrel (n=685)	Clopidogrel (n=678)	HR (95% CI)	Prasugrel (n=685)	Clopidogrel (n=678)	HR (95% CI)
	n (%) [*]	n (%) [*]		n (%) [*]	n (%) [*]	
Overall bleeding events	341 (49.8)	247 (36.4)	1.48 (1.25–1.74)	115 (16.8)	103 (15.2)	1.09 (0.83–1.42)
Major TIMI bleeding	13 (1.9)	15 (2.2)	0.82 (0.39–1.73)	4 (0.6)	6 (0.9)	0.64 (0.18–2.27)
Life-threatening bleeding	4 (0.6)	7 (1.0)	0.54 (0.16–1.85)	1 (0.1)	4 (0.6)	0.24 (0.03–2.16)
Fatal bleeding	2 (0.3)	1 (0.1)	1.77 (0.16–19.54)	1 (0.1)	1 (0.1)	0.90 (0.06–14.45)
Minor TIMI bleeding	27 (3.9)	15 (2.2)	1.76 (0.94–3.31)	7 (1.0)	6 (0.9)	1.10 (0.37–3.27)
Clinically relevant bleeding	29 (4.2)	39 (5.8)	0.72 (0.44–1.16)	24 (3.5)	35 (5.2)	0.66 (0.39–1.11)
Other bleeding	298 (43.5)	209 (30.8)	1.51 (1.26–1.80)	85 (12.4)	67 (9.9)	1.24 (0.90–1.71)
Major or minor TIMI bleeding	39 (5.7)	29 (4.3)	1.30 (0.81–2.11)	11 (1.6)	12 (1.8)	0.87 (0.38–1.97)
Major, minor, or clinically relevant bleeding	66 (9.6)	65 (9.6)	0.98 (0.70–1.38)	34 (5.0)	45 (6.6)	0.72 (0.46–1.13)
Bleeding events leading to discontinuation	16 (2.3)	20 (2.9)	0.76 (0.40–1.48)	9 (1.3)	12 (1.8)	0.72 (0.30–1.71)

^{*}Incidence (%)=n for each bleeding event/n for each group (prasugrel or clopidogrel)×100%.

TIMI, thrombolysis in myocardial infarction. Other abbreviations as in Table 2.

in the prasugrel group and 11.8% (95% CI 9.5–14.5) in the clopidogrel group. The HR was 0.77 (95% CI 0.56–1.07), corresponding to a risk reduction (1–HR) of 23% for prasugrel (Figures 2,3).

During the first 24 weeks of the study, the incidence of non-fatal MI, the most frequent MACE, was 7.6% in the prasugrel group and 10.1% in the clopidogrel group. The HR was 0.74 (95% CI 0.52–1.06). The incidence of cardiovascular death was 1.3% in the prasugrel group and 0.9% in the clopidogrel group, and the incidence of nonfatal stroke was 0.4% in the prasugrel group and 1.0% in the clopidogrel group. The incidence of stent thrombosis (0.4% vs. 0.7%) and of revascular-

ization (4.6% vs. 4.8%) was similar in the prasugrel and clopidogrel groups. In the subgroup analysis of MACE at 24 weeks, there were no subgroups with significantly worse outcomes in the prasugrel group than in the clopidogrel group (Table 2, Figure 3). The incidence of stent thrombosis at 24 weeks was similar in both groups, irrespective of whether the patient received a bare metal stent (0.6% vs. 0.8%) or a drug-eluting stent (0.3% vs. 0.7%). The type/brand of stent did not influence the incidence of MACE in either group (data not shown).

There were slight increases in the overall incidence of MACE and of each component between 24 and 48 weeks. The HRs for MACE and its components at 48 weeks were similar

Figure 4. Rates of primary efficacy endpoints in the present (PRASFIT-ACS) study and in TRITON-TIMI 38. The incidence of the primary efficacy endpoint (major adverse cardiac events [MACE]) and the hazard ratios were similar between the 2 studies. Modified from Ruff et al.¹²

to those at 24 weeks (Table 2).

The incidence of MACE from the first dose until 14 days after the last dose was similar to that at 24 weeks (Table 2). The incidence of cardiovascular death up to 14 days after the last dose was 0.6% in the prasugrel group and 0.8% in the clopidogrel group. Post hoc analyses of the efficacy endpoints through to week 24 and until 14 days after the last dose confirmed that the incidence of cardiovascular death was similar between the 2 groups (data not shown).

Bleeding Events

Table 3 shows the incidence of non-CABG-related bleeding events that occurred up until 14 days after the last dose in both groups. Major bleeding events, which were the key safety endpoint in TRITON-TIMI 38, occurred in 1.9% (13/685) of patients treated with prasugrel and in 2.2% (15/678) of patients treated with clopidogrel. The incidences of major spontaneous bleeding and life-threatening bleeding events were similar in both groups. Only 2 patients treated with prasugrel and 1 patient treated with clopidogrel had a fatal major bleeding event. We also examined the incidence of bleeding events in subgroups of patients with a high risk of bleeding, as reported in TRITON-TIMI 38,⁶ namely those aged ≥ 75 years or weighing ≤ 60 kg. In the present study, the incidence of major bleeding among patients aged ≥ 75 years (3.6% [6/165] vs. 4.1% [6/148]) or those weighing ≤ 60 kg (3.4% [9/266] vs. 3.8% [9/240]) was comparable between the prasugrel and clopidogrel groups. We also examined the incidence of major bleeding in the subgroup of patients weighing ≤ 50 kg, which was defined as low body weight in the Japanese Phase II study (unpublished data). The incidence of major bleeding was 5.9% (5/85) in the prasugrel group and 2.8% (2/72) in the clopidogrel group, but the incidence of spontaneous major bleeding was very low in both groups (2.4% [2/85] vs. 1.4% [1/72]).

The incidence of major or minor bleeding events, which was the key safety endpoint in the Japanese Phase II trial, was 5.7% (39/685) in the prasugrel group and 4.3% (29/678) in the clopidogrel group, but the incidence of spontaneous bleeding

events with non-external causes was similar in both groups (1.6%, [11/685] vs. 1.8%, [12/678]). Regarding the incidences of major or minor bleeding events with external causes, complications of PCI occurred in 2.8% and 1.8% of patients in the prasugrel and clopidogrel groups, respectively, with other causes noted in 1.3% and 0.7% of patients in the prasugrel and clopidogrel groups, respectively.

The incidences of non-CABG-related major, minor, or clinically relevant bleeding, and bleeding events leading to discontinuation were similar in both groups.

AEs

Treatment-emergent AEs occurred in 89.8% (615/685) of patients treated with prasugrel and in 88.5% (600/678) of patients treated with clopidogrel (Table S1). Serious AEs occurred in 27.4% (188/685) and 25.4% (172/678) of patients treated with prasugrel and clopidogrel, respectively. AEs requiring drug withdrawal occurred in 7.9% (54/685) and 9.0% (61/678) of patients treated with prasugrel and clopidogrel, respectively. AEs related to the study drug that occurred in $\geq 5\%$ of patients in both groups were bleeding-related events (Table S1).

Discussion

In this study, we confirmed that the HR for the prasugrel 20/3.75 mg group relative to the clopidogrel 300/75 mg group was <1.0 for the incidence of MACE (HR 0.77, 95% CI 0.56–1.07), corresponding to a risk reduction of 23% for prasugrel.

To show superiority of a drug relative to a comparator, it is usually necessary to enroll a large number of patients, especially if an active comparator is being used. Indeed, in TRITON-TIMI 38, more than 13,000 patients were enrolled to compare the efficacy and safety of prasugrel and clopidogrel. For the present study, however, it was not possible to enroll a sufficient number of Japanese patients to achieve a sample size that would be able to detect statistical superiority. However, prasugrel achieved a significant reduction in the incidence of

MACE compared with clopidogrel in the ACS patients in TRITON-TIMI 38. Although the present study and TRITON-TIMI 38 differed in terms of the prasugrel dosing regimen and the follow-up period, both studies were fairly similar in terms of disease setting, inclusion criteria, and primary endpoint. Furthermore, the clopidogrel dosing regimen was identical and most MACE occurred before 24 weeks in TRITON-TIMI 38. The same trend was observed in a Japanese ACS registry.¹¹ For these reasons, we determined whether the HR for prasugrel relative to clopidogrel was <1.0 for the incidence of MACE at 24 weeks by determining point estimates. As shown in **Figure 4**, the incidence of MACE in the PRASFIT-ACS study using the lower dose of prasugrel of 20/3.75 mg was similar to that in TRITON-TIMI 38.¹² The incidence of MACE at 24 weeks in both groups in the present study seemed to be slightly higher than in TRITON-TIMI 38. The present study included greater proportions of patients aged ≥ 75 years and patients with multiple lesions treated with the first PCI compared with TRITON-TIMI 38. The incidence of MACE in each of these subgroups was higher in the results of blind review; thus, these differences between the 2 trials might explain the differences in the incidence of MACE. However, most MACE occurred in the first 24 weeks of TRITON-TIMI 38, and the HR obtained in the PRASFIT-ACS study (HR 0.77, 95% CI 0.56–1.07) was similar to that obtained in the overall cohort of TRITON-TIMI 38 (HR 0.81, 95% CI 0.73–0.90). In addition, the HR in the overall cohort and the HR at 180 days were similar in TRITON-TIMI 38 (data not shown). Based on these results, we considered the efficacy of prasugrel in the PRASFIT-ACS study was similar to that shown in the TRITON-TIMI 38 study. This trend for the incidence of MACE in the prasugrel group was maintained throughout the 24 weeks of treatment and until the end of the 48-week treatment period.

We determined the composite endpoint used in TRITON-TIMI 38,⁶ with the exception of nonfatal non-ischemic stroke. In TRITON-TIMI 38, MACE included nonfatal stroke irrespective of the presence/absence of ischemia.⁶ Based on the pharmacological effects of thienopyridines, we excluded nonfatal non-ischemic stroke from the primary efficacy endpoint. Because nonfatal non-ischemic stroke occurred in only 1 patient, who was treated with clopidogrel, exclusion of this component did not affect the primary efficacy outcome. Consequently, the incidence of the primary endpoint in our study was comparable with that in TRITON-TIMI 38.

The incidence of cardiovascular death during the first 24 weeks in our study was 1.3% in the prasugrel group and 0.9% in the clopidogrel group. However, the incidence of cardiovascular death until 14 days after the last dose was similar in both treatment groups. This difference in cardiovascular mortality was because of 6 deaths that occurred >14 days after switching from prasugrel to clopidogrel or from prasugrel to no drug treatment. Based on these results, we must be careful when interpreting the incidence of cardiovascular death in both treatment groups.

The adjusted dosing regimen for Japanese patients should minimize the risk of bleeding. The incidence of non-CABG-related major bleeding and the incidence of major, minor, or clinically relevant bleeding was almost the same in the prasugrel and clopidogrel groups. In TRITON-TIMI 38, prasugrel resulted in a significantly higher incidence of major bleeding compared with clopidogrel, but this trend was not observed in the PRASFIT-ACS study, even though the incidence of major or minor bleeding events was 5.7% in the prasugrel group and 4.3% in the clopidogrel group. In addition, the incidence of

spontaneous major or minor bleeding events was almost the same in both groups (1.6% vs. 1.8%). In the subgroup analysis of patients aged ≥ 75 years or weighing ≤ 60 kg, which were identified as risk factors in TRITON-TIMI 38, the incidence of major bleeding was similar between the prasugrel and clopidogrel groups. Among patients weighing ≤ 50 kg, which was defined as low body weight in the Japanese Phase II study, the incidence of major bleeding was 5.9% in the prasugrel group and 2.8% in the clopidogrel group, but the incidence of spontaneous major bleeding was very low in both treatment groups. Therefore, we consider that the adjusted dosing regimen for Japanese patients minimizes the risk of bleeding.

The incidence of treatment-emergency AEs was similar in both treatment groups. AEs related to the study drug occurred in just under half of the patients in both groups, but all of the events that occurred in $\geq 5\%$ of patients in both groups were bleeding-related events (eg, subcutaneous bleeding and nosebleeds). In almost all cases, patients recovered with appropriate treatment.

As shown in **Figure 3**, none of the subgroups showed significantly worse outcomes in the prasugrel group than in the clopidogrel group. Therefore, we considered that the efficacy of prasugrel in the prespecified subgroups was consistent with that in the overall cohort of the PRASFIT-ACS study. However, unexpectedly, the direction of the HR was opposite in patients with and without diabetes mellitus. The HR was 1.39 (95% CI 0.80–2.40) in patients with diabetes mellitus and 0.57 (95% CI 0.37–0.87) in patients without diabetes mellitus. The incidence of MACE in patients in the clopidogrel group with and without diabetes mellitus was 9.7% and 12.9%, respectively, which was quite different from previous reports.^{6,13,14} However, in the prasugrel group, the incidence of MACE in patients with diabetes mellitus was similar to that described in previous studies, including the TRITON-TIMI 38 study.⁶ Although it is difficult to provide a clear explanation for these findings, we suspect the small sample size of the subgroups may have contributed.

We need antiplatelet drugs to reduce ischemic events. However, an increase in platelet inhibition may increase the risk of bleeding. In the PRASFIT-ACS study, the adjusted dosing regimen of prasugrel for Japanese patients provided similar efficacy to that reported in TRITON-TIMI 38, without an increased risk of bleeding compared with clopidogrel. We think that the main contributor to these outcomes of the PRASFIT-ACS study was the use of an adjusted dosing regimen of prasugrel that balances the benefits and possible risks of prasugrel in Japanese patients.

Study Limitations

The main limitation of this study was the relatively small sample size. It was not feasible to conduct a clinical trial in Japan that could enroll a sufficient number of patients to detect statistical superiority or non-inferiority of prasugrel relative to clopidogrel for the incidence of MACE. This issue might explain why the 95% CIs for some comparisons (eg, MACE through to week 24 or 48) included 1. However, the present study is the largest Japanese clinical trial to date of patients with ACS undergoing PCI, and the results are similar to those reported in TRITON-TIMI 38 based on prespecified point estimates of MACE for the prasugrel and clopidogrel groups.

Another limitation of the present study is that we excluded patients with a history of stroke and/or TIA. In TRITON-TIMI 38, patients with these conditions did not benefit from prasugrel treatment because they tended to experience more major bleeding events; therefore, we considered that such patients should

not be included for prasugrel treatment in the present study. Nevertheless, this factor should be taken into account when comparing the results of this study with those of TRITON-TIMI 38.

Conclusions

A prasugrel dosing regimen (LD/MD: 20/3.75 mg) that was adjusted for Japanese patients with ACS undergoing PCI was associated with a low incidence of MACE, similar to the results of TRITON-TIMI 38, and with a low risk of clinically serious bleeding in Japanese ACS patients.

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Disclosures

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Supplementary Files

Supplementary File 1

List of Institutions That Participated in or Helped Implement the PRASFIT-ACS Study

Table S1. Treatment-emergent AEs in Japanese patients with acute coronary syndrome undergoing percutaneous coronary intervention

Please find supplementary file(s);
<http://dx.doi.org/10.1253/circj.CJ-13-1482>