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ORIGINAL ARTICLE

Multicenter research of bleeding risk between prasugrel and clopidogrel in Japanese patients with coronary artery disease undergoing percutaneous coronary intervention

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Abstract

Although it has been reported that prasugrel achieves stronger antiplatelet effect and fewer cardiovascular events compared to clopidogrel in Japanese patients, there are limited data comparing the safety between the 2 dose regimens. Data from 1031 consecutive patients with coronary artery disease undergoing PCI at 5 institutions from May 2014 to April 2016, who received aspirin plus either clopidogrel (619 patients) or prasugrel (412 patients), were retrospectively analyzed. The choice of clopidogrel or prasugrel was left to the operator's discretion. Adverse events were defined as a composite of bleeding, hepatopathy, leukopenia, thrombopenia, exanthema, and major adverse cardiovascular events (MACE). MACE was defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal ischemic stroke. The average follow-up period was 143 days in the prasugrel group and 263 days in the clopidogrel group. Adverse events occurred in 34.5% of patients in the prasugrel group and in 28.6% in the clopidogrel group. Although the Kaplan–Meier curves showed lower survival rates from MACE, all-bleeding, major bleeding, minor bleeding, and adverse events, in the prasugrel group compared to the clopidogrel group (log rank test $p=0.009$, $p=0.001$, $p=0.012$, $p=0.018$, and $p<0.001$, respectively), multivariate Cox-regression analyses determined prasugrel as a significant risk factor for all-bleeding, minor bleeding, and adverse events, but not for MACE and major bleeding events. Dual antiplatelet therapy with prasugrel was independently associated with minor bleeding events, but not with MACE and major bleeding events, compared to clopidogrel, after PCI in common clinical settings.

Keywords Antiplatelet therapy · Hemorrhage · Clopidogrel · Percutaneous coronary intervention · Prasugrel

Introduction

As the number of ischemic heart disease IHD) patients has been increasing in Asian countries including Japan, percutaneous coronary intervention PCI) has been widely used in recent decades. Since stent deployment is performed in most PCI cases, dual antiplatelet therapy DAPT) is essential for prevention of stent thrombosis. Recent improvements in stent technology, especially newer generation drug-eluting stents DES), have shortened the duration of DAPT compared to the early DES era [1, 2]. However, some clinical trials have realized the importance of long-term DAPT in specific patients at high risk for cardiovascular events [3]. Therefore, those results have recently raised concerns about the safety of DAPT after PCI.

Although clopidogrel has been widely used for DAPT after stent implantation, its interpatient variability of

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pharmacodynamic response due to genetic polymorphism of CYP2C19 is well known, and is reportedly frequent in Japanese patients [4–6]. Prasugrel has a different metabolic pathway from that of clopidogrel, and the difference in efficacy among individuals is smaller than clopidogrel [7–9]. Considering the higher average age, lower body weight, and increased bleeding risk with other thrombotic agents in Japanese patients, lower loading and maintenance doses of prasugrel have been established in Japan compared to those in Western countries [10]. Previously, Prasugrel Compared with Clopidogrel for Japanese Patients with ACS Undergoing PCI PRASFIT-ACS) and Prasugrel for Japanese Patients with Coronary Artery Diseases Undergoing Elective PCI PRASFIT-Elective) trials showed an equivalent incidence of bleeding events between low-dose prasugrel and standard-dose clopidogrel [11, 12]. However, since both were phase III trials, which excluded patients at high risk of bleeding, the results may not reflect real-world clinical settings. Thus, the aim of this study was to evaluate the risk of adverse events, especially bleeding events, induced by prasugrel compared to clopidogrel in Japanese patients who underwent PCI in common clinical settings.

Materials and methods

Patient population

A total of 1465 consecutive patients aged over 20 years old with coronary artery disease undergoing PCI at Chiba Aoba Municipal Hospital, Chiba Kaihin Municipal Hospital, Kimitsu Chuo hospital, Matsudo City Hospital, and Chiba University Hospital from May 2014 to April 2016 were retrospectively analyzed. Patients with any of the following were excluded: (1) prescription of prasugrel or clopidogrel more than 1 month before first PCI; (2) switching P2Y12 inhibitors within 2 weeks for any reason; (3) no prescription of DAPT; (4) prescription of ticlopidine as a P2Y12 inhibitor; (5) no follow-up data available over 2 weeks; (6) no documentation of P2Y12 inhibitors dosage; (8) need for emergent surgery after PCI; and (9) self-interruption of P2Y12 inhibitors. The protocol was approved by the Institutional Research Board of each participating center. This study was registered at University hospital Medical Information Network (UMIN) with the UMIN number of UMIN000029481.

Antiplatelet therapy

All patients with acute coronary syndrome (ACS) were administrated either loading dose (LD) of 20 mg prasugrel or 300 mg clopidogrel before or during PCI. Patients undergoing elective PCI were also administrated LD of P2Y12 inhibitors as necessary before PCI. The choice of clopidogrel or prasugrel was left to the operator's discretion. Maintenance dose (MD) of P2Y12 inhibitors was 3.75 mg for prasugrel and 75 mg for clopidogrel. Aspirin (100 mg once daily) was administered, in addition to P2Y12 inhibitors.

Clinical outcomes

Major adverse cardiovascular events MACE) were defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal ischemic stroke within follow-up periods. Bleeding was classified by the Bleeding Academic Research Consortium BARC) definition [13]. The non-coronary artery bypass grafting (CABG)-related major bleeding event (BARC type 3 and 5) was regarded as major bleeding in the present study. Adverse events were defined as a composite of bleeding, hepatopathy, leukopenia, thrombopenia, exanthema, and MACE within follow-up periods. These events were collected from any medical records available.

Statistical analysis

Categorical variables were reported as counts (percentage) and Chi square test was used for comparison. Continuous variables were reported as mean ± standard deviation and Student *t* test was used for comparison. All statistical analyses were performed two-sided at the 0.05 level of significance using EZR [14]. Primary endpoint was analyzed as the full analysis set divided into the prasugrel group and the clopidogrel group. The incidence rate of MACE and adverse events were calculated in each group. The survival rate from MACE or adverse events in each group was estimated using the Kaplan–Meier method. Risk factors of MACE or adverse events were also estimated using Cox-regression analysis.

Results

A total of 1031 eligible patients who received either prasugrel (412 patients) or clopidogrel (619 patients) were enrolled (Fig. 1). The average follow-up period was 139 ± 125 days in the prasugrel group and 238 ± 186 days in the clopidogrel group. Overall, 76.6% of the patients were male, mean age was 69.9 years, and 36.0% were > 75 years old. The mean body weight was 63.6 ± 13.2 kg, and 26.7% were less than 50 kg. Patient characteristics for each group are shown in Table 1. The prevalence of hypertension and prior MI was lower in the prasugrel group than in the clopidogrel group (66.7% vs. 75.0%, $p < 0.01$; 8.3% vs. 12.6%, $p = 0.03$, respectively). Acute coronary syndrome was more common in the

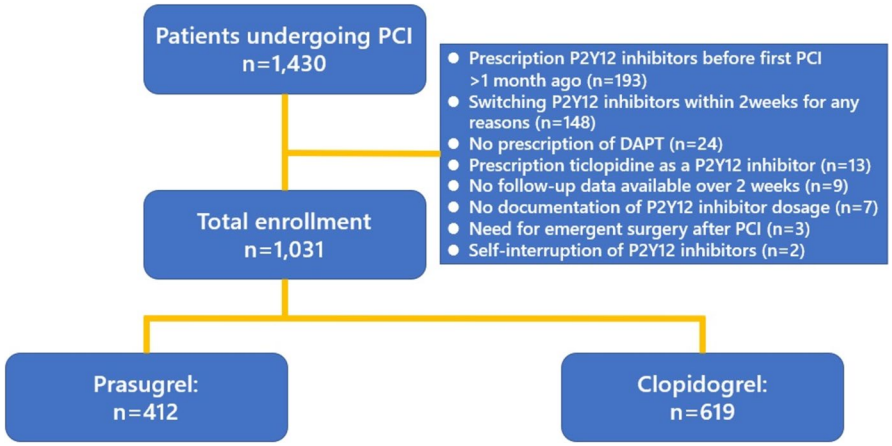

Fig. 1 Patients enrolment

prasugrel group than in the clopidogrel group (68.7% vs. 40.7%, $p < 0.01$). Drug-eluting stents were used with similar frequency in both groups (96.1% vs. 93.7%, $p = 0.91$). As concomitant therapies, proton-pump inhibitors were used more often (93.0% vs. 88.5%, $p = 0.02$), and anticoagulant therapy (7.8% vs. 13.2%, $p < 0.01$), especially warfarin (3.9% vs. 7.4%, $p = 0.02$), was used less often in the prasugrel group compared to the clopidogrel group.

Table 2 shows the incidence of each component of adverse events. Adverse events occurred in 34.5% of patients in the prasugrel group and in 28.6% in the clopidogrel group. The Kaplan–Meier curves showed a lower survival rate from MACE and cardiovascular death (the main component of MACE) at 12 months in the prasugrel group compared to the clopidogrel group (90.1% vs. 95.9%, $p < 0.01$ and 91.1% vs. 96.8%, $p < 0.01$). However, the Cox regression analyses did not determine prasugrel as a significant risk factor for MACE Table 3 and cardiovascular death [HR 1.50 (95% CI 0.78–2.91)]. In terms of bleeding, the Kaplan–Meier curves showed lower survival rates from all-bleeding, major bleeding, and minor bleeding events in the prasugrel group compared to the clopidogrel group (Figs. 2, 3, log rank test $p = 0.001$, $p = 0.012$, $p = 0.018$, respectively). Cox regression analyses determined prasugrel as a significant risk factor for all-bleeding and minor bleeding events, but not for major bleeding events (Tables 4, 5, 6). In ACS patients, the incidence of major bleeding was 9.9% and 8.3%, whereas in non-ACS patients, it was 3.8% and 2.7%, in the prasugrel and clopidogrel groups, respectively. Finally, the Kaplan–Meier curves showed a lower survival rate from adverse events in the prasugrel group compared to the clopidogrel group (Fig. 3, log rank test $p < 0.001$). Cox regression analyses determined prasugrel as a significant risk factor for adverse events. Definite/probable stent thrombosis was observed in 1 case in the prasugrel group (0.2%) and 2 cases (0.3%) in the clopidogrel group. All stent thromboses occurred within 30 days after implantation, and no late or very late stent thrombosis was detected.

Discussion

The present study revealed that the incidences of adverse events and all-bleeding events, especially minbleeding events, were significantly higher in patients under DAPT with low-dose prasugrel compared to standard-dose clopidogrel after PCI in common clinical settings, while those of MACE and majbleeding events were not.

The incidence of MACE was 9.4% and 11.8% in the prasugrel and clopidogrel groups in the PRASFIT-ACS study, and 4.1% and 6.7% in the PRASFIT-Elective study [11, 12]. In the present study, MACE occurred 6.5% and 4.1% in the prasugrel and clopidogrel groups, respectively. Although Kaplan–Meier curves of MACE showed a lower survival rate in the prasugrel group compared to the clopidogrel group, Cox-regression analysis did not determine prasugrel as an independent risk factor for MACE. This result may have been resulted from the higher rate of ACS in the prasugrel group, which was a strong confounding factor contributing to the incidence of MACE, particularly cardiovascular death. Considering that ACS patients comprised 68.7% and 40.7% in the prasugrel and clopidogrel groups, this result seems permissible in real-world clinical settings. In terms of cardiovascular death, the PRASFIT-ACS study reported an incidence of 2.1% and 2.4% in the prasugrel and clopidogrel groups, whereas in ours, it was 5.6% and 3.1% in the prasugrel and clopidogrel groups [11]. The reason for the relatively higher rate of cardiovascular death in our study is believed to be attributable to higher patient comorbidities, such as cardiopulmonary arrest (5.6% and 2.9% in the prasugrel and clopidogrel groups), Killip's classification IV (8.5% and 5.5%), and end-stage renal disease (7.8% and

Table 1 Clinical features of patients enrolled

Clinical features	Prasugrel ($n=412$)	Clopidogrel ($n=619$)	p value
Male	313 (76.0)	477 (77.1)	0.69
Age (years)	69.5 ± 11.6	70.1 ± 10.8	0.61
≥ 75 years old	144 (35.0)	227 (36.7)	0.57
Body weight (kg)	63.5 ± 13.4	63.6 ± 13.1	0.88
< 50 kg	117 (28.4)	158 (25.5)	0.31
Body mass index (kg/m^2)	23.9 ± 4.6	24.1 ± 3.8	0.35
Current smoker	118 (28.6)	175 (28.3)	0.90
Hypertension	275 (66.7)	464 (75.0)	< 0.01
Dyslipidemia	238 (57.8)	383 (61.9)	0.19
Diabetes mellitus	163 (39.6)	256 (41.4)	0.57
Pror iMI	34 (8.3)	78 (12.6)	0.03
Pror iCABG	6 (1.4)	21 (3.4)	0.06
eGFR (mL/min/m^2)	61.0 ± 21.8	62.7 ± 21.0	0.20
< 30	33 (8.0)	41 (6.6)	0.40
30–50	81 (19.7)	112 (18.1)	0.53
Heart failure	53 (12.9)	90 (14.5)	0.45
ACS	283 (68.7)	252 (40.7)	< 0.01
STEMI	210 (51.0)	191 (30.9)	< 0.01
Killip I	126 (30.6)	124 (20.0)	< 0.01
Killip II	21 (5.1)	21 (3.4)	0.18
Killip III	28 (6.8)	12 (1.9)	< 0.01
Killip IV	35 (8.5)	34 (5.5)	0.06
UA/NSTEMI	73 (17.7)	61 (9.9)	< 0.01
No. of treated lesion sites	1.57 ± .79	1.51 ± .75	0.31
Stent type			
Bare metal	9 (2.2)	15 (2.4)	0.80
Drug-eluting	396 (96.1)	580 (93.7)	0.91
Concomitant therapy			
Proton-pump inhibit	383 (93.0)	548 (88.5)	0.02
Statin	356 (86.4)	499 (81.5)	0.15
Steroids	17 (4.1)	20 (3.2)	0.45
Anticoagulant therapy	32 (7.8)	82 (13.2)	< 0.01
Warfarin	16 (3.9)	46 (7.4)	0.02
Directal anticoagulants	16 (3.9)	36 (5.8)	0.16

Values are n (%) or mean ± standard deviation

ACS acute coronary syndrome, *CABG* coronary artery bypass grafting, *eGFR* estimated glomerular filtration rate, *MI* myocardial infarction, *NSTEMI* non-*ST*-segment elevation myocardial infarction, *STEMI* ST-segment elevation myocardial infarction, *UA* unstable angina

6.6%), included in our study, which were excluded in the PRASFIT-ACS study.

In the present study, the prasugrel group showed a significantly higher incidence of adverse events compared to the clopidogrel group, which was mainly derived from the significantly higher incidence of all-bleeding events. In the PRASFIT-ACS study, the higher rate of all-bleeding events was observed in the prasugrel group compared to the clopidogrel group [49.8% vs. 36.4%, HR 1.48 (95% CI 1.25–1.74)] [11]. In PRASFIT-Elective study, all-bleeding events occurred in 38.1% and 34.4% of patients in the prasugrel and clopidogrel groups, but the statistical significance was not described [12]. Our study demonstrated that the incidence of all-bleeding events was 32.5% and 27.3% in the prasugrel and clopidogrel groups, and use of prasugrel was one of the independent risk factors. Compared to the previous PRASFIT studies, the incidence of all-bleeding events was relatively lower in the present study [11, 12]. This discrepancy might be caused by underestimation of the event rate, especially minor bleeding events, due to the retrospective analysis of our study. Regarding the major bleeding, it was confirmed that prasugrel was not independently associated with increase in major bleeding events in the

Table 2 Details of adverse events

Adverse events	Prasugrel ($n=412$)	Clopidogrel ($n=619$)	Details of bleeding	Prasugrel ($n=412$)	Clopidogrel ($n=619$)
Adverse events	142 (34.5)	177 (28.6)	BARC ≤ 2	101 (24.5)	138 (22.3)
MACE	27 (6.5)	25 (4.0)	BARC > 2	33 (8.0)	31 (5.0)
Cardiovascular death	23 (5.6)	19 (3.1)	Type of bleeding		
Non-fatal MI	1 (0.2)	1 (0.2)	Intracranial bleeding	3 (0.7)	3 (0.5)
Non-fatal ischemic stroke	3 (0.7)	5 (0.8)	Gastrointestinal bleeding	26 (6.3)	33 (5.3)
Bleeding	134 (32.5)	169 (27.3)	Access-site related bleeding	55 (13.3)	77 (12.4)
Hepatopathy	3 (0.7)	6 (1.0)	Subcutaneous bleeding	27 (6.6)	34 (5.5)
Leukopenia	1 (0.2)	2 (0.3)	Rhinrhagia	16 (3.9)	14 (2.3)
Thrombopenia	4 (1.0)	3 (0.5)	Hematuria	12 (2.9)	14 (2.3)
Exanthema	5 (1.2)	7 (1.1)	Other bleeding	7 (1.7)	19 (3.1)

Incidence (%) = *n* for each bleeding event/n for each group (prasugrel or clopidogrel) × 100%. Other abbreviations as in Table 1

BARC bleeding academic research consortium, *MACE* major adverse cardiac events

Table 3 Univariate and multivariate Cox-regression analysis of variables associated with MACE

Fact	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Diabetes mellitus	0.90 (0.50–1.63)	0.73		
eGFR < 30 mL/min/m^2	1.71 (0.80–3.70)	0.17		
Heart failure	3.70 (1.92–7.13)	< 0.01	2.88 (1.59–5.23)	< 0.01
Prior MI	2.12 (1.00–4.50)	0.05	1.68 (0.81–3.50)	0.17
Age ≥ 75	1.40 (0.75–2.59)	0.29		
Sex (female vs male)	1.07 (0.50–2.30)	0.86		
Indication (ACS vs non-ACS)	4.70 (2.13–10.40)	< 0.01	4.48 (2.08–9.64)	< 0.01
Body weight < 50 kg	0.92 (0.44–1.91)	0.82		
P2Y12 inhibit (prasugrel vs clopidogrel)	1.41 (0.78–2.55)	0.25		
Majbleeding events	8.33 (3.97–17.50)	< 0.01	6.83 (3.76–12.47)	< 0.01

Other abbreviations as in Table 1 and 2

HR hazard ratio, *CI* confidence interval

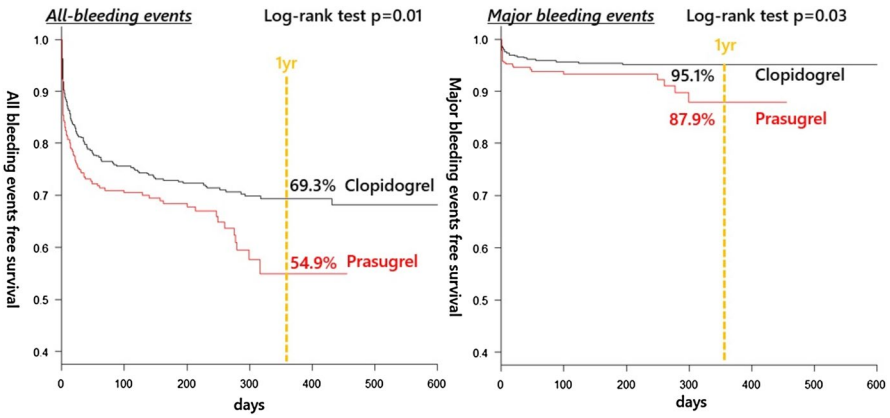

Fig. 2 Survival rates from all-bleeding and major bleeding events

present study, as similarly observed in the PRASFIT studies [11, 12, 15]. In the PRASFIT-ACS study, there were no significant differences in the incidence of major bleeding events between the prasugrel and clopidogrel groups (6.3% vs. 5.5%, $p = 0.654$) [11]. In the PRASFIT-Elective study, the incidence of major bleeding was 2.7% and 3.2% in the prasugrel and

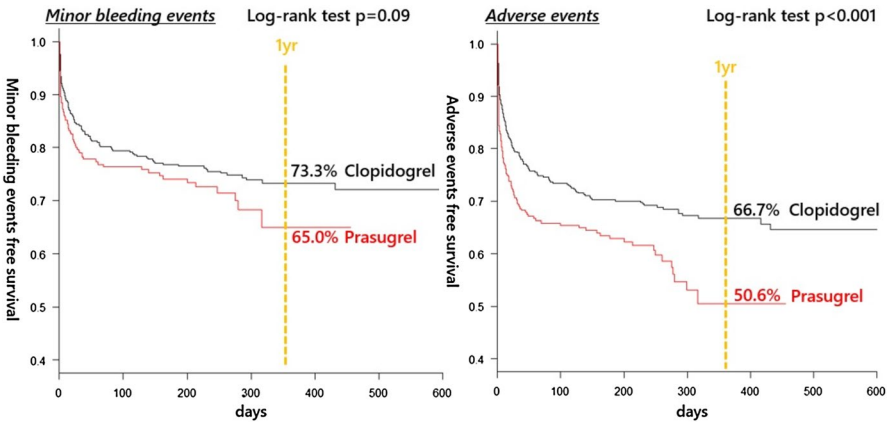

Fig. 3 Survival rates from minor bleeding and adverse events

Table 4 Univariate and multivariate Cox-regression analysis of variables associated with all-bleeding events

Fact	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Hypertension	1.17 (0.90–1.52)	0.23		
Diabetes mellitus	0.80 (0.63–1.01)	0.06	0.82 (0.65–1.04)	0.10
eGFR < 30 mL/min/m^2	1.31 (0.87–1.96)	0.20		
Prior MI	1.30 (0.91–1.85)	0.15	1.28 (0.90–1.81)	0.17
Age ≥ 75 years	1.32 (1.03–1.69)	0.03	1.35 (1.06–1.72)	0.02
Sex (female vs male)	1.03 (0.77–1.38)	0.84		
Indication (ACS vs non-ACS)	1.01 (0.79–1.28)	0.95		
Body weight < 50 kg	1.27 (0.95–1.70)	0.10	1.34 (1.04–1.73)	0.03
Steroids	1.68 (1.05–2.71)	0.03	1.75 (1.10–2.80)	0.02
Oral anticoagulants	1.60 (1.14–2.23)	< 0.01	1.55 (1.11–2.15)	< 0.01
P2Y12 inhibit (prasugrel vs clopidogrel)	1.52 (1.19–1.94)	< 0.01	1.48 (1.18–1.87)	< 0.01

Abbreviations as in Tables 1 and 3

Table 5 Univariate and multivariate Cox-regression analysis of variables associated with major bleeding events

Fact	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Hypertension	1.29 (0.73–2.28)	0.38		
Diabetes mellitus	0.95 (0.58–1.55)	0.83		
eGFR < 30 mL/min/m^2	4.47 (2.47–8.06)	< 0.01	5.35 (3.04–9.40)	< 0.01
Age ≥ 75 years	1.12 (0.66–1.91)	0.68		
Prior MI	0.89 (0.38–2.10)	0.79		
Sex (female vs male)	0.55 (0.29–1.07)	0.08	0.58 (0.30–1.10)	0.10
Indication (ACS vs non-ACS)	2.88 (1.57–5.28)	< 0.01	3.41 (1.91–6.10)	< 0.01
Body weight < 50 kg	2.43 (1.35–4.37)	< 0.01	2.14 (1.30–3.52)	< 0.01
Steroids	2.22 (0.93–5.28)	0.03	2.13 (0.91–4.99)	0.08
Oral anticoagulants	1.72 (0.91–3.26)	0.09	1.68 (0.90–3.16)	0.10
P2Y12 inhibit (prasugrel vs clopidogrel)	1.39 (0.84–2.33)	0.20		

Abbreviations as in Tables 1 and 3

clopidogrel groups no statistical evaluation) [12]. The present study demonstrated the relatively higher incidence of major bleeding events in ACS patients 9.9% and 8.3% in the prasugrel and clopidogrel groups) compared to the PRASFIT-ACS study, although the similar incidence in non-ACS patients was observed 3.8% and 2.7%) as with the PRASFIT-Elective study, and prasugrel was not an independent risk factor for overall major bleeding events [11, 12]. This result might be caused

Table 6 Univariate and multivariate Cox-regression analysis of variables associated with minor bleeding events

Fact	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Hypertension	1.13 (0.84–1.51)	0.41		
Diabetes mellitus	0.79 (0.61–1.04)	0.09	0.79 (0.61–1.04)	0.09
eGFR < 30 mL/min/m^2	0.64 (0.33–1.21)	0.17		
Age ≥ 75 years	1.40 (1.06–1.84)	0.02	1.48 (1.15–1.92)	< 0.01
Prior MI	1.33 (0.90–1.96)	0.15		
Sex (female vs male)	1.26 (0.91–1.74)	0.17		
Indication (ACS vs non-ACS)	0.80 (0.61–1.05)	0.11		
Body weight < 50 kg	1.06 (0.79–1.49)	0.72		
Steroids	1.70 (0.96–3.00)	0.07	1.83 (1.05–3.20)	0.03
Oral anticoagulants	1.55 (1.04–2.31)	0.03	1.42 (0.96–2.11)	0.08
P2Y12 inhibit (prasugrel vs clopidogrel)	1.57 (1.19–2.07)	< 0.01	1.39 (1.07–1.80)	0.01

Abbreviations as in Tables 1 and 3

by the ACS patients with severe conditions enrolled in our study, which were excluded in the PRASFIT-ACS study. With regard to minor bleeding, the significantly higher incidence in the prasugrel group compared to the clopidogrel group was reported in the PRASFIT-ACS study [11]. Similarly, our study demonstrated that prasugrel was independently associated with increase in minor bleeding events. These results suggested that, although prasugrel was associated with higher incidence of all-bleeding events than clopidogrel, it was mainly derived from the increase in minor bleeding events, and the incidence of clinically problematic major bleeding events seemed to be more reflective of real-world clinical settings, particularly in ACS patients.

The combined data of PRASFIT-ACS and PRASFIT-Elective studies showed that the risk factors for the composite endpoint of major, minor, and clinically relevant bleedings were ACS, female, low body weight (≤ 50 kg), and the elderly (≥ 75 years) [16]. Our data determined ACS, low body weight (≤ 50 kg), and renal failure (≤ 30 mL/min/m^2), as the risk factors for major bleeding. ACS was a strong contributor to bleeding events consistently in the PRASFIT-ACS and PRASFIT-Elective studies, and in the present study [16]. In the TRITON-TIMI 38 trial, STEMI was one of the independent risk factors for serious bleeding. These results demonstrate that ACS status often includes patients with severe vulnerable conditions for adverse events, including bleeding [17]. Other factors presented in the PRASFIT studies and ours were reasonable contributors to bleeding, which were previously reported.

Study limitations

The present study has several limitations. First, this was a retrospective study, raising a possibility of deficit in data about clinical events, especially minor bleeding events. Second, this was a non-randomized study, which included selection bias. Third, while prasugrel was approved in May 2014 in Japan, there was a limitation to the prescription duration for 2 weeks until May 2015. This affected the selection of prasugrel or clopidogrel between May 2014 and May 2015, resulting in the shorter follow-up period of prasugrel than clopidogrel. Lastly, long-term clinical outcomes were not clear in this study. However, most patients have recently discontinued DAPT at 6–12 months after PCI. Thus, further study is required to clarify this issue.

In conclusion, dual antiplatelet therapy with low-dose prasugrel was independently associated with all bleeding events, especially minbleeding events, but not with other clinical events, including MACE and majbleeding, compared to standard-dose clopidogrel in Japanese patients after PCI in real-wld clinical settings.

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Compliance with ethical standards

Conflict of interest Yoshio Kobayashi has received fees from Daiichi-Sankyo and Sanofi. The other auths rept no conflicts.

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