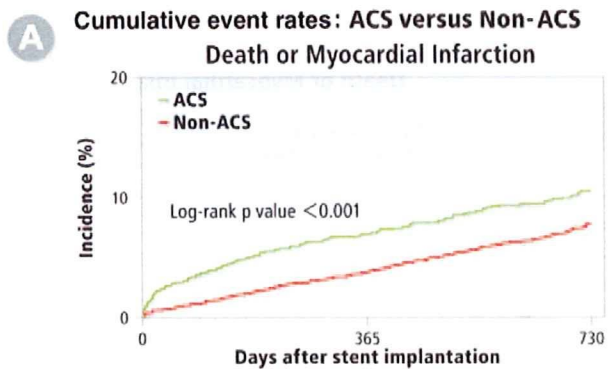
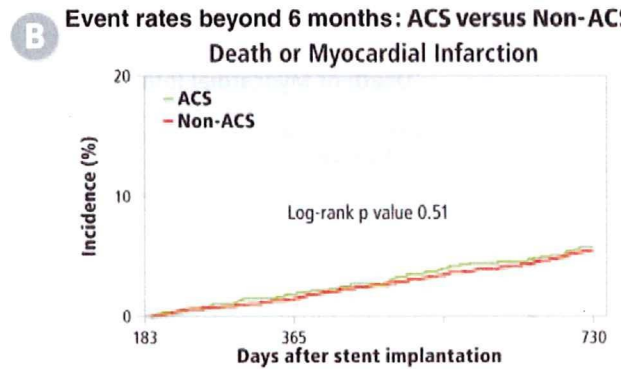
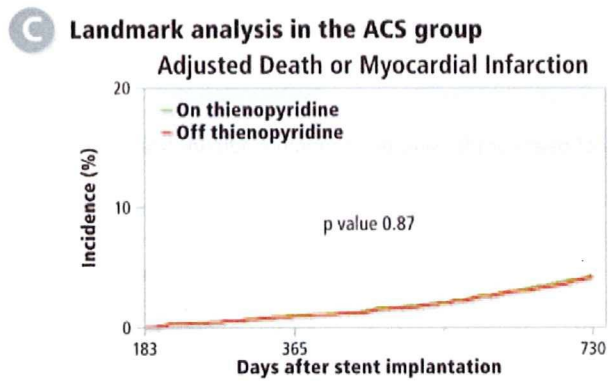


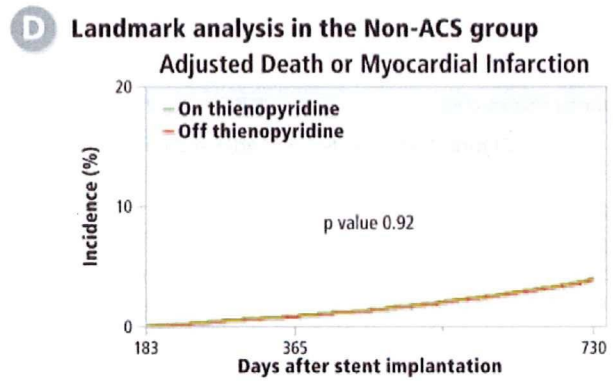
Days after stent implantation	0	183	365	730
Cumulative incidence, ACS		5.1%	6.9%	10.4%
Number of events		116	157	194
Number of patients at risk	2308	2132	2018	650
Cumulative incidence, Non-ACS		2.1%	3.7%	7.7%
Number of events		179	307	483
Number of patients at risk	8470	8162	7816	2932



Days after stent implantation	183	365	730
Cumulative incidence, ACS		1.9%	5.7%
Number of events		38	75
Number of patients at risk	2025	1919	627
Cumulative incidence, Non-ACS		1.5%	5.5%
Number of events		116	284
Number of patients at risk	7850	7532	2850



Days after stent implantation	183	365	730
Cumulative incidence, On thienopyridine		1.3%	4.2%
Number of events		31	55
Number of patients at risk	1447	1364	438
Cumulative incidence, Off thienopyridine		1.3%	4.1%
Number of events		7	20



Days after stent implantation	183	365	730
Cumulative incidence, On thienopyridine		1.1%	3.9%
Number of events		84	213
Number of patients at risk	5800	5554	1967
Cumulative incidence, Off thienopyridine		1.1%	4.0%
Number of events		32	71

Figure 4. A, Cumulative rates of death or MI in patients with or without ACS. B, Rates of death or MI beyond 6 months in patients with or without ACS. C and D, Adjusted cumulative incidences of death or MI using the 6-month landmark analysis in patients with and without ACS.

Despite these limitations, we would conclude that discontinuation of both thienopyridine and aspirin, but not discontinuation of thienopyridine therapy alone, was associated with an increased risk of ST. Landmark analysis did not suggest an apparent clinical benefit of thienopyridine use beyond 6 months after SES implantation.

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Disclosures

Dr Kimura serves as an advisory board member and member of the speakers' bureau for Cordis Cardiology and has received honoraria from Cordis Cardiology. Dr Nakagawa is a member of the speakers' bureau and has received honoraria from Cordis Cardiology. Dr Miyazaki is an advisory board member and receives honoraria from Cordis Cardiology. Drs Shiode and Mitsudo both report receipt of honoraria from Cordis Cardiology. The remaining authors report no conflicts.

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CLINICAL PERSPECTIVE

Randomized data are lacking on the optimal duration of dual-antiplatelet therapy after drug-eluting stent implantation and on the risks associated with discontinuation of dual-antiplatelet therapy. Despite the absence of randomized data, the use of dual-antiplatelet therapy beyond 1 year has become commonplace in clinical practice. In the j-Cypher registry, 10 778 Japanese patients treated exclusively by sirolimus-eluting stents were followed up for up to 2 years with prospective data collection on the status of antiplatelet therapy during follow-up. Incidences of definite stent thrombosis were 0.34% at 30 days, 0.54% at 1 year, and 0.77% at 2 years. Thienopyridine use was maintained in 97%, 62%, and 50% of patients at 30 days, 1 year, and 2 years, respectively. The main findings of the present study were that discontinuation of both aspirin and thienopyridine, but not discontinuation of thienopyridine therapy only, was associated with an increased stent thrombosis risk and that no apparent clinical benefit of thienopyridine use could be seen beyond 6 months after sirolimus-eluting stent implantation, according to the 6-month landmark analysis. Given the increased risk of bleeding and huge economic burden associated with prolonged dual-antiplatelet therapy, the optimal duration of dual-antiplatelet therapy should be defined by prospective randomized trials evaluating its net clinical benefit after consideration of both ischemic events and bleeding complications.

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Clopidogrel Resistance in Japanese Patients Scheduled for Percutaneous Coronary Intervention

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Background Dual antiplatelet therapy with acetylsalicylic acid (ASA) and a P2Y12 ADP-receptor blocker is standard for prevention of coronary stent thrombosis. Clopidogrel, a 2nd-generation P2Y12 blocker, has recently become available in Japan and this study aimed to evaluate its antiplatelet effects in Japanese patients.

Methods and Results Thirty Japanese patients scheduled for elective coronary stent implantation were enrolled. Under low-dose ASA therapy, 300 mg clopidogrel was loaded on the 1st day and a daily 75-mg dose was administered on the following days. Assessed by optical aggregometer, rapid inhibition occurred at 4 h, when the inhibition of platelet aggregation rate (IPA) was 16.4±12.8% using 5 μmol/L ADP as the stimulus. The antiplatelet efficacy of clopidogrel was reasonably constant in each patient throughout the study period, although there was a broad inter-individual variation. At 48 h after clopidogrel loading, the ratios of responders (IPA ≥30%), hypo-responders (10%≤IPA<30%), and non-responders (IPA <10%) were 36%, 50%, and 14%, respectively.

Conclusions The antiplatelet effectiveness of clopidogrel appeared individual-specific with wide inter-individual variation. The rate of clopidogrel non-responders was 14% among the examined Japanese patients. (*Circ J* 2009; **73:** 336–342)

Key Words: Adenosine diphosphate; Antiplatelet drug; Clopidogrel; Coronary stent; Thienopiridine

Percutaneous coronary intervention (PCI) with coronary stent implantation is performed worldwide for ischemic heart disease. In Japan, 153,501 patients underwent this therapy in 2006, as described in the surveillance report from the Japan Circulation Society. One of the most serious problems is acute and late thrombosis at the site of stenting and much effort had been made to avoid this critical complication. The current standard dual antiplatelet therapy with acetylsalicylic acid (ASA) and thienopyridine ADP-receptor blocker has proven to be a powerful preventive solution.[1–5]

Two thienopyridine antiplatelet agents are currently available: ticlopidine and clopidogrel. Although ticlopidine, a 1st-generation thienopyridine, has contributed much to the prevention of stent thrombosis, it frequently causes adverse side-effects such as agranulocytosis, thrombotic thrombocytopenic purpura and liver injury. Clopidogrel, a 2nd-generation P2Y12 blocker, has a better safety profile with a lower incidence of hematologic and liver complications, and has now largely replaced ticlopidine in clinical practice.

One important problem with clopidogrel is the wide inter-individual variation in its antiplatelet effect.[3,6–8] It has been demonstrated that clopidogrel does not exert an antiplatelet effect in a certain proportion of patients in Western populations,[9] known as clopidogrel resistance. Importantly, several studies have revealed that cardiovascular risk is elevated in patients with clopidogrel resistance.[10]

On the other hand, there are well-established differences in the atherothrombotic and hemorrhagic risks in the Japanese compared with Western populations,[11] so results from clinical trials in the West using novel antithrombotic agents cannot be applied directly to Japanese patients. Furthermore, the standard dose of ticlopidine for the Japanese (200 mg/day) is much lower than that for Western people (500 mg/day), but the same daily maintenance dose (75 mg) of clopidogrel is used in both populations. Therefore, some Japanese physicians are concerned about the strength of the effect of clopidogrel in Japanese patients and because of those concerns, we designed the present study to evaluate the antiplatelet effects of clopidogrel under low-dose ASA therapy in 30 Japanese patients scheduled for PCI.

Methods

Study Protocol

This study was approved by the Ethics Committee of Kyoto University Hospital, and written informed consent was given by all enrolled patients, who were undergoing elective

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coronary stent implantation. The initial diagnosis of ischemic heart disease was based on symptoms, a non-invasive examination such as stress electrocardiogram, and/or coronary computed tomography angiography. Further entry criteria were (1) ASA (81–100 mg/daily) for at least 7 days prior to the initial cardiac catheterization and (2) platelet count of 100–350×10^9/L and hemoglobin ≥10 g/dl. Exclusion criteria were: (1) recent bleeding diathesis; (2) hematologic or malignant disorder; (3) oral anticoagulation with coumarin derivatives; (4) glycoprotein IIb/IIIa inhibitor or fibrinolytics administered during either the PCI or the preceding 14 days; and (5) antiplatelet therapy with thienopyridines, cilostazol or dypridimole within the preceding 28 days.

A loading dose of 300 mg clopidogrel was administered on the 1st day, approximately 24 h before PCI. A daily maintenance dose (75 mg) was administered the morning before the procedure and continued thereafter. ASA was administered at a daily dose of 81–100 mg. Blood samples were collected at enrolment, and at 4 (3–5) h, 24 (22–26) h and 48 (46–50) h after the loading dose (**Table 1**). The 24-h sampling was performed before the daily 75 mg clopidogrel intake, whereas the 48-h sampling was afterward. All 30 enrolled patients were to be evaluated until 48 h after the loading dose; 9 patients did not undergo PCI because of unexpectedly mild stenosis and re-evaluation of the PCI indication on the following day and therefore, those patients discontinued clopidogrel intake. PCI was carried out in the remaining 21 patients and their blood samples were analyzed on days 14 (12–16) and 28 (26–30).

Analysis of Platelet Aggregation

Blood samples were collected using a 21G needle, with tourniquet, into a glass tube containing a final solution of 0.313% sodium citrate. Platelet-rich plasma (PRP) was prepared by centrifugation at 150 g at 25°C for 15 min and platelet-poor plasma was prepared by centrifugation at 1,740 g at 25°C for 10 min. The PRPs were stimulated by 5 and 20 μmol/L ADP (adenosine diphosphate; Chronolog), and 2 μg/ml collagen (Horm, Germany) at 37°C and the aggregations were analyzed, under stirring, using a 12-channel light transmission aggregometer (MCM HEMA TRACER 313; MC Medical, Japan), whereby the degree of light transmission of the PRP was defined as 0% of the aggregation rate and the cognitive platelet-poor plasma as 100%.[12,13] The degree of light transmission was monitored for 10 min after agonist stimulation and platelet aggregation was evaluated. All the procedures were completed within 2 h of blood sampling. The maximal aggregation rate (MAR) and the inhibition of platelet aggregation (IPA), which was calculated as the percent inhibition of baseline aggregation according to the following equation, were evaluated:

$$IPA(\%) = \{(MAR_{baseline} - MAR_{time\ after\ treatment})/MAR_{baseline}\} \times 100.$$

Table 1 Study Protocol

		Platelet function analysis
Day 0	*Clopidogrel 300 mg*	*1) Baseline* *2) 4 h after loading*
Day 1	*Clopidogrel 75 mg*	*3) 24 h after loading* *4) 48 h after loading*
Day 28	↓	*5) 14 days after loading* *6) 28 days after loading*

Analysis of Vasodilator-Stimulated Phosphoprotein (VASP) Phosphorylation

The VASP is an abundant substrate of cAMP-dependent protein kinase in platelets. Its phosphorylation levels were measured using the Platelet VASP-FCM kit (Biocytex Inc, Marseille, France) in which the VASP-phosphorylation levels are quantified by flow cytometry after stimulation of whole blood with prostaglandin E_1 (PGE_1; mean fluorescence intensity (MFI)) and also PGE_1 plus ADP (MFI PGE_1 + ADP). The $P2Y_{12}$ reactivity index (PRI), calculated as percent inhibition of baseline aggregation was evaluated according to the following equation:

$$PRI = \{(MFI_{PGE_1} - MFI_{PGE_1+ADP})/MFI_{PGE_1}\} \times 100.$$

Table 2 Baseline Characteristics

	Total (n=30)	*PCI (n=21)*	*Non-PCI (n=9)*	*P (PCI vs non-PCI)*
Age (years)	*70±7*	*71±9*	*68±3*	*0.11*
Males	*22 (73%)*	*17 (81%)*	*5 (56%)*	*0.16*
Platelets (×10⁴/μl)	*21.1±5.5*	*20.4±5.2*	*22.2±5.8*	*0.43*
Risk factors				
Current smoker	*10 (33%)*	*11 (52%)*	*0 (0%)*	*0.0013*
Hyperlipidemia[1]	*22 (73%)*	*18 (86%)*	*5 (56%)*	*0.083*
Diabetes[2]	*7 (23%)*	*6 (29%)*	*1 (11%)*	*0.28*
Hypertension[3]	*18 (60%)*	*15 (71%)*	*4 (44%)*	*0.16*
Prior myocardial infarction	*1 (3%)*	*1 (5%)*	*0 (0%)*	*0.39*
Prior PCI	*4 (13%)*	*3 (14%)*	*1 (11%)*	*0.81*
Prior cerebrovascular event	*1 (3%)*	*1 (5%)*	*0 (0%)*	*0.39*
Peripheral vascular disease	*2 (7%)*	*2 (10%)*	*0 (0%)*	*0.22*
Treatment				
β-blocker	*4 (13%)*	*3 (14%)*	*1 (11%)*	*0.81*
Nitrates	*7 (23%)*	*5 (24%)*	*2 (22%)*	*0.92*
ACEI/ARB	*13 (43%)*	*8 (38%)*	*5 (56%)*	*0.38*
Statin	*26 (87%)*	*19 (90%)*	*7 (78%)*	*0.35*
Ca-channel blocker	*15 (50%)*	*12 (57%)*	*3 (30%)*	*0.23*
Proton pump inhibitor	*7 (23%)*	*5 (24%)*	*2 (22%)*	*0.92*

Defined as [1]under medical treatment or total cholesterol level >220 mg/dl or low-density cholesterol level >140 mg/dl, [2]HbA_{1c} >6.5%, [3]systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg.
PCI, percutaneous coronary intervention; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II-receptor blocker.

Table 3 Maximal Aggregation Rates (%)

	Baseline	*4 h*	*24 h*	*48 h*	*14 days*	*28 days*
ADP (5 μmol/L) stimulation						
Total (n=30)	*64.5±6.7 (30)*	*53.8±10.1 (29)*	*52.9±8.9 (30)*	*49.0±10.2 (28)*		
PCI-treated (n=21)	*65.5±5.9 (21)*	*54.7±10.3 (20)*	*53.6±8.6 (21)*	*49.2±9.8 (20)*	*46.8±12.5 (20)*	*48.8±11.0 (21)*
PCI-untreated (n=9)	*62.0±8.2 (9)*	*52.0±10.0 (9)*	*52.0±10.0 (9)*	*48.6±11.8 (8)*		
ADP (20 μmol/L) stimulation						
Total (n=30)	*72.0±6.2*	*63.1±10.6*	*62.7±10.0*	*59.9±11.1 (28)*		
PCI-treated (n=21)	*72.8±6.5*	*63.8±10.7*	*62.7±9.6*	*60.1±11.4 (20)*	*55.8±10.2 (20)*	*57.0±10.3 (21)*
PCI-untreated (n=9)	*70.0±5.4*	*61.8±8.5*	*62.7±8.5*	*58.4±10.9 (8)*		
Collagen (2 μmol/L) stimulation						
Total (n=30)	*49.3±16.1*	*36.8±16.9*	*36.7±14.2*	*36.1±15.9 (28)*		
PCI-treated (n=21)	*50.3±15.8*	*40.1±16.8*	*38.3±13.2*	*37.7±14.2 (20)*	*33.1±12.2 (20)*	*34.8±11.9 (21)*
PCI-untreated (n=9)	*47.0±17.5*	*29.4±15.3*	*32.8±16.4*	*32.4±17.5 (8)*		

Abbreviation see in Table 2.
The number of examined subjects is shown in parentheses.

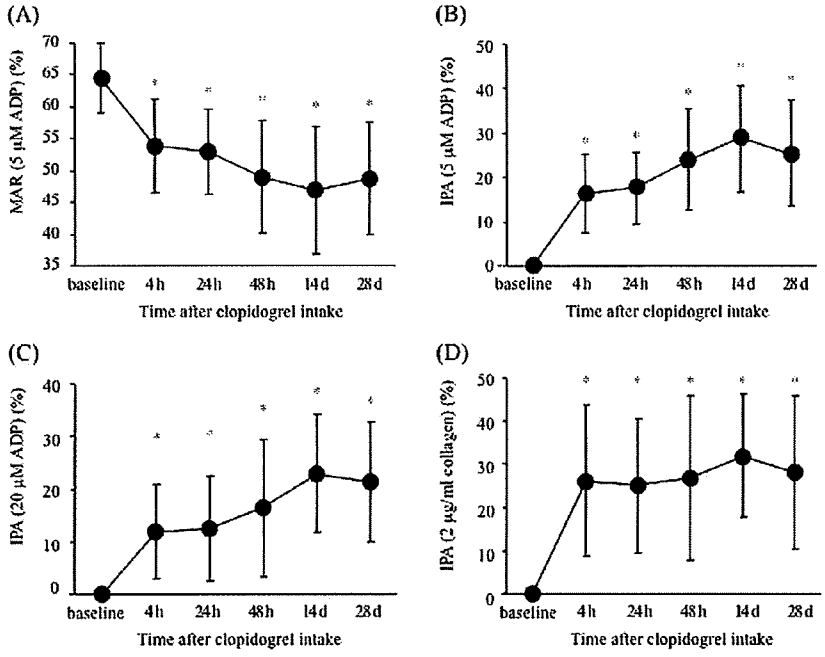

Fig 1. Time-dependent change in platelet aggregation after clopidogrel intake. (**A**) Maximal aggregation rates (MARs) induced with 5 μmol/L ADP. (**B**) Inhibition of platelet aggregations (IPAs) with 5 μmol/L ADP stimulation. (**C**) IPAs with 20 μmol/L ADP stimulation; (**D**) IPAs with 2 μg/ml collagen stimulation. By 1-sample t-test compared with the data at baseline, *P<0.0001.

Definition of Clopidogrel Responsiveness

Classification of clopidogrel effectiveness was based on the definition from a previous report:[14] IPA<10% (clopidogrel non-responders); 10%≤IPA<30% (hypo-responders); IPA≥30% (responders).

Statistic Analysis

Continuous variables are expressed as mean±SD. Categorical variables are expressed as frequencies and percentages. Comparisons between categorical variables were performed using 2-tailed Fisher's exact test or the Pearson's chi-square test. Student's t-test was used to compare continuous variables. Changes in parameters were analyzed using 1-sample t-test. A P-value <0.05 was defined as statistical significance. Statistical analyses were performed using StatView 5.0 software (SAS Institute, Cary, NC, USA).

Results

Characteristics of the Study Population

The baseline characteristics of the 30 enrolled patients are shown in **Table2**. Mean age was 70±7 years and 22 patients (73%) were male. Only 1 patient (3%) had a history of prior myocardial infarction and 4 (13%) had undergone a prior PCI. Among the 30 patients, 9 did not undergo PCI because of unexpectedly mild stenosis on coronary angiography, which was not apparent on the initial non-invasive assessment. In the others (n=21), PCI with Cypher-stent® implantation was successfully performed. Blood examination was performed until 48 h after intake of 300 mg clopidogrel for all 30 patients, and additionally, on days 14 and 28 post-procedure for the 21 patients undergoing PCI. Because some patients did not cooperate, and other administrative reasons, a few data points were not available. The number of patients evaluated for platelet function was as follows: at 4 h (n=29), 24 h (n=30), and 48 h (n=28) after clopidogrel intake (n=30), and at 14 days (n=20) and 28 days (n=21) among patients undergoing PCI (n=21) (**Table3**). In all 30 enrolled patients, we did not observe any haematologic disorders or liver dysfunction during the study period.

Baseline characteristics were not significantly different between the PCI (n=21) and non-PCI (n=9) groups, apart from smoking habit (**Table2**). As shown in **Table3**, there was no significant difference between the 2 groups in the

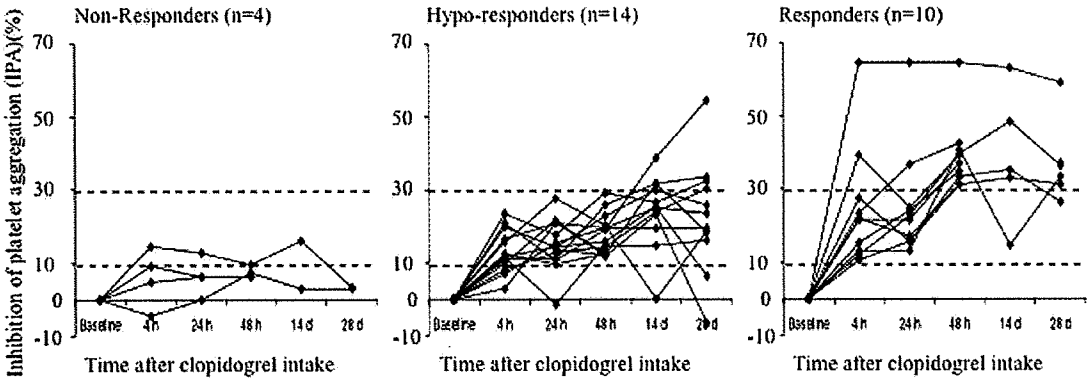

Fig 2. Time-dependent change in the inhibition of platelet aggregation (IPA) after clopidogrel intake for each subject categorized as a responder, hypo-responder or non-responder based on the IPAs with 5μmol/L ADP stimulation at 48 h after clopidogrel intake, as described in the Methods.

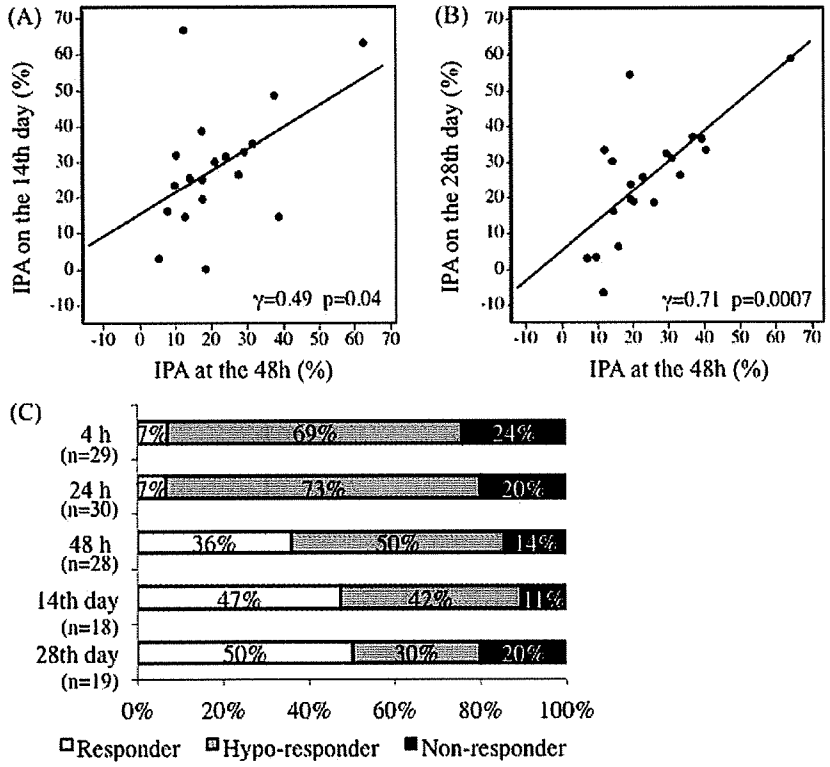

Fig 3. Correlation of the inhibition of platelet aggregation (IPA) with 5μmol/L ADP at 48 h with values from the 14th day (**A**, n=18) or the 28th day (**B**, n=19) and (**C**) time-dependent change in the ratios of responders, hypo-responders and non-responders at 4 h, 24 h, 48 h, on the 14th day, and on the 28th day after clopidogrel intake using 5μmol/L ADP as a stimulus are shown according to the definition: IPA<10% as non-responder, 10% ≤IPA<30% as hypo-responder and IPA ≥30%.

ADP-induced MAR at baseline or at 4, 24 or 48 h. Therefore, both groups were analyzed together.

Platelet Aggregation

The MARs induced by 5μmol/L ADP time-dependently decreased after clopidogrel intake (**Fig 1A**), and the IPA values, which represent the degree of inhibition of platelet aggregability, increased reciprocally (**Fig 1B**). After 300-mg clopidogrel loading, rapid inhibition occurred at 4 h (IPA= 16.4±12.8%, P<0.0001 vs baseline), which continued until 24 h (IPA=17.6±12.1%, P<0.0001 vs baseline). Following 75-mg clopidogrel intake, platelet aggregability was inhibited more intensely after 48 h (IPA=24.0±13.9%, P<0.0001 vs 4 h and P<0.001 vs 24 h). It was noted that IPA did not attain a steady state within 24 h after the initial 300-mg clopidogrel intake. The same trend was observed with 20μmol/L ADP (**Fig 1C**), for which the IPAs after clopidogrel intake were 11.9±13.6% at 4 h, 12.4±13.9% at 24 h, 16.3±16.3% at 48 h, 22.9±14.5% at 14 days, and 21.3±14.9% at 28 days. These data obtained with 5 or 20μmol/L ADP stimulation suggest that clopidogrel efficiently exhibited antiplatelet effects and that a 300-mg loading dose might not be immediately sufficient to obtain the maximal antiplatelet effect.

Furthermore, clopidogrel intake also inhibited collagen-stimulated platelet aggregation (**Fig 1D**): IPAs after clopidogrel intake were 26.2±22.4% (4 h), 25.0±19.9% (24 h), 26.8± 22.8% (48 h), 31.7±19.0% (14 days), and 29.5±24.9% (28 days).

Rates of Clopidogrel Responders and Non-Responders

We analyzed the inter-individual variation in 5μmol/L ADP-induced platelet aggregability. Individual plots of the IPAs are shown in **Fig 2**. The effectiveness of clopidogrel exhibited a wide inter-individual variation and was quite constant in individual patients throughout the study period. The effects of clopidogrel were examined on the 14th and

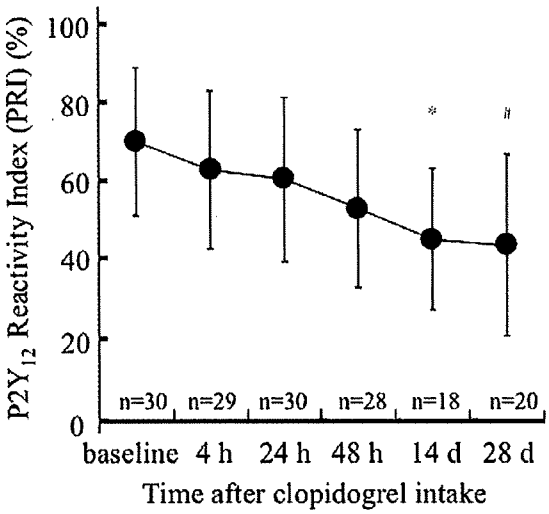

Fig 4. Time-dependent inhibition of P2Y12 reactivity index (PRI), calculated with data based on vasodilator-stimulated phosphoprotein phosphorylation as described in the Methods, at baseline, and at 4 h, 24 h, 48 h, 14th day, and 28th day after clopidogrel intake. By 1-sample t-test compared with data at baseline, *P<0.0001, #P<0.001.

28th days in 21 patients undergoing PCI. Among these patients, the IPAs at 48 h with 5 μmol/L ADP correlated well with those on the 14th day (P=0.04, r=0.49, n=18; **Fig 3A**) and the 28th day (P=0.0007, r=0.71, n=19; **Fig 3B**).

The proportion of responders, hypo-responders, and non-responders at 4 h with 5 μmol/L ADP was 7%, 69%, and 24%, respectively, and 36%, 50%, and 14%, respectively, at 48 h, indicating that the antiplatelet effects of clopidogrel at 48 h were stronger than those at 4 h, although we observed a rapid effect of clopidogrel at 4 h with the 300-mg loading dose. After 48 h, the antiplatelet effects of clopidogrel appeared to reach a plateau (**Figs 1,2**). The rates of non-responders at 48 h, on the 14th day, and on the 28th day were 14%, 11%, and 20%, respectively, while the rates of responders were 36%, 47%, and 50% (**Fig 3C**).

Clopidogrel Responses Evaluated by VASP Phosphorylation

VASP is an abundant substrate of cAMP-dependent protein kinase in platelets. Binding of ADP to P2Y12 leads to Gi-coupled inhibition of adenylate cyclase, causing reduction of cAMP and the VASP-phosphorylation level in platelets. When P2Y12 receptors are successfully blocked by clopidogrel, the addition of ADP will not reduce the PGE1-indiuced VASP phosphorylation levels. Using these principles, VASP phosphorylation levels were evaluated by flow cytometry in the present study and the PRI was used to evaluate clopidogrel's efficacy: the lower the PRI, the stronger the clopidogrel antiplatelet effect through inhibition of the P2Y12 receptor.

As shown in **Fig 4**, the PRIs gradually decreased after clopidogrel intake in a time-dependent manner: 70.2±19.0% at baseline, 62.9±20.4% at 4 h, 60.4±21.2% at 24 h, 52.9±20.0% at 48 h, 44.9±18.2% on day 14, and 43.8±23.9% on day 28. The PRIs and the IPAs at 48 h after clopidogrel intake were negatively correlated with each other (γ=0.67).

Discussion

In this study, we evaluated the antiplatelet effect of clopidogrel under low-dose ASA therapy in Japanese patients scheduled for PCI, and found that there was a wide inter-individual variation and that the effects in Japanese may not be as strong as for Caucasians at the same dose.

We noted that the effectiveness of clopidogrel was reasonably constant in each patient throughout the study period (**Fig 3**), indicating that responsiveness is individual-specific. In a Western population, the rates of patients with so called 'clopidogrel resistance' ranged between 5% and 44%, although the definitions of clopidogrel resistance varied[9] As shown in **Fig 3**, we also detected 4 (14%) non-responders at 48 h and in 1 patient (3%), clopidogrel suppressed ADP-induced platelet aggregability strongly at 4 h and throughout the study period. These data suggest that there is also a wide variety of responses to clopidogrel in the Japanese.

We used the definition of clopidogrel response proposed by Angiollilo et al because their study design was similar to ours, except that their patients took a higher dose of 250 mg ASA (vs 81–100 mg in our study) and platelet aggregation was evaluated with the optical aggregometer with 6 μmol/L ADP stimulation (vs 5 μmol/L ADP in our study)[14] Therefore, the MAR at baseline in our study (64.5±4.5%) was equivalent to theirs (approximately 60–62%)[14] Importantly, the ratio of responders at 4 h after a 300-mg loading dose was much lower in our study than in their study (7% vs 48%, respectively) and was also the case at 48 h, because the ratios of responders were 36% vs 80%, respectively. Another study conducted in Sweden demonstrated that the mean IPA with 20 μmol/L ADP was approximately 30% at 4 h after a 300-mg loading dose under 325 mg ASA therapy;[15] whereas the IPA with 20 μmol/L ADP in our study was 12%. Thus, the degree of platelet inhibition in the Japanese obtained with a similar regimen of clopidogrel, in which a 300-mg loading dose and 75-mg maintenance dose were administered under ASA therapy, might be lower than that in Western populations.

PRI values based on the VASP phosphorylation levels are becoming widely used for the evaluation of the antiplatelet effects of clopidogrel[16,17] We also found them useful because clopidogrel significantly inhibited the PRIs. Using the same loading/maintenance clopidogrel regimen, Grossmann et al report that 10 (17.5%) of 57 patients were inadequate responders (PRI >50%) at 5 days[17] In the present study, the percentages of inadequate responders (RPI >50%) were 16/28 (57%) at 48 h, 10/20 (50%) at 14 days, and 7/21 (33%) at 28 days. Based on these results, we again consider that, at the present dosage, the antiplatelet effect of clopidogrel in the Japanese was not as strong as for Westerners.

Thus, on average, the antiplatelet effects of clopidogrel in Japanese patients are not as strong as those observed in Western people receiving a similar regimen of a 300-mg loading dose followed by a daily 75-mg maintenance dose under ASA therapy. To answer the question whether 75 mg/day clopidogrel is too strong for Japanese, we would answer that, based on the data presented here, it is not the case. Rather, the relatively weaker antiplatelet effect of clopidogrel in Japanese compared with in Western people might cause a higher incidence of stent thrombosis. However, currently we have no data on the degree of antiplatelet effect by clopidogrel that is necessary for the prevention of stent thrombosis in Japanese patients. Furthermore, because little data are available concerning the effect of ticlopidine in Japanese that would be sufficient to prevent stent thrombosis, we cannot conclude that the antiplatelet effect of clopidogrel at the current dosage is insufficient to prevent stent thrombosis. Further study is essential to link the effec-

tiveness of clopidogrel to the clinical outcomes of Japanese patients.

Our study clearly revealed that there are some clopidogrel non-responders among Japanese patients and thus their risk of stent thrombosis would be high. One possible solution could be to add cilostazol to the dual antiplatelet therapy of ASA and clopidogrel, because the functional mechanism of cilostazol, a phosphodiestrase 3 inhibitor, is partly similar to that of clopidogrel toward increasing the cAMP concentration in platelets[5,18] and its addition would enhance the antiplatelet effects of the dual antiplatelet therapy[19,20]

The mechanisms of clopidogrel resistance are considered to involve both acquired and genetic factors[21] Clopidogrel is a pro-drug, which needs to be activated to become the active substance through the action of Cyp3A4 and Cyp2C19. Single nucleotide polymorphisms (SNPs) in Cyp2C19 have been suggested as causes of resistance[22–24] There is an inter-ethnic variability in the rate of the Cyp2C19 SNPs that cause Cyp2C19 to be non-functional and approximately 20% of Japanese people have been reported to possess little Cyp2C19 activity in contrast to only 2.5% of Westerners[25] Therefore, a genetic defect in Cyp2C19 might have a great influence on clopidogrel effectiveness in the Japanese. Further examination is required.

Concomitant treatment with drugs metabolized by Cyp2C19 and Cyp3A4 might reduce the antiplatelet effect of clopidogrel. The proton-pump inhibitor, omeprazole, which is metabolized by Cyp2C19, has been reported to reduce clopidogrel efficacy[26] In our study, only 3 patients were treated with omeprazol and their IPAs at 48h using 5μmol/L ADP were 6.0%, 14.5%, and 15.9%, respectively. Because the average IPA was 24.0±13.9% among 28 patients, the IPAs in the omeprazol-treated patients tended to be lower (P=0.12, vs IPAs in omeprazol-free patients). A Cyp3A4 metabolizing drug, atorvastatin, has also been reported to affect clopidogrel's efficacy[27] although other reports showed no effects[28,29] In our study, IPA with 5μmol/L ADP at 48h was 21.2±10% (P=0.53, vs IPAs in atorvastatin-free patients), suggesting that atorvastatin might not affect the antiplatelet effects of clopidogrel; however, our study was small-scale, so further study with a larger number of patients is essential for drawing conclusions concerning these drug interactions.

We observed a clear reduction of the collagen-induced platelet aggregability by clopidogrel intake under dual antiplatelet therapy with ASA (**Fig 1D**). Collagen may induce aggregation mainly via the ADP pathway under ASA therapy. In other words, the signaling pathway stimulated by collagen might be shifted to the $P2Y_{12}$ ADP-receptor pathway in platelets under ASA therapy, in which platelets cannot adequately generate thomboxane A_2.

Evaluation of the antiplatelet effects of clopidogrel has been performed using several modalities, such as VerifyNow[30] and PFA100[31] both of which are whole-blood aggregometers, in addition to the optical aggregometer and analysis of VASP phosphorylation used in the present study. Further, the definition of clopidogrel resistance varies in each study. Thus, the method and definition used to evaluate the effect of clopidogrel have not yet been established, which would enable comparison of studies.

In summary, we showed that the antiplatelet effect of clopidogrel varied in Japanese patients, with 14% non-responders, and that, on average, the effect was not as strong as that observed in Western patients with a similar regimen of a 300-mg loading dose followed by a daily 75-mg maintenance dose under ASA therapy.

Acknowledgements

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Letter to the Editor

Sudden cardiac death after PCI and CABG in the bare-metal stent era: Incidence, prevalence, and predictors☆

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Abstract

Background: Few prospective cohort studies have examined the relationship between reduced left ventricular ejection fraction (LVEF) and other comorbidities for precise risk stratification of sudden cardiac death (SCD) after coronary revascularization.
Methods: We analyzed 9877 consecutive patients who underwent first elective percutaneous coronary intervention (PCI) ($n=6878$) and coronary artery bypass grafting (CABG) ($n=2999$) between 2000 and 2002 at 30 institutions registered under the CREDO-Kyoto registry.
Results: During the long-term follow-up (median follow-up period=42.8 months), 906 patients (9.4%) died; death from cardiovascular causes was observed in 517 (5.7%) patients; cardiac death, in 376 (3.9%) patients; and SCD, in 140 (1.5%) patients. The rates of SCD were 0.5%, 0.9%, and 1.3% at 1, 2, and 3 years of follow-up, respectively. Multivariate analyses indicated that dialysis (hazard ratio=2.51), chronic obstructive pulmonary disease (hazard ratio=2.04), congestive heart failure (hazard ratio=1.63), reduced LVEF (LVEF ≤ 30%; hazard ratio=1.55), chronic total occlusion of coronary artery (hazard ratio=1.38), diabetes with insulin therapy (hazard ratio=1.33), chronic renal disease (hazard ratio=1.29), and peripheral artery disease (hazard ratio=1.27) were independent predictors of SCD.
Conclusions: The method of revascularization had no influence on the incidence of SCD, and the adjusted hazard ratio of reduced LVEF was smaller than that observed in dialysis, chronic obstructive pulmonary disease, and congestive heart failure. This indicated that the risk of SCD depends on multiple variables in addition to LVEF.

Keywords: Sudden cardiac death; Percutaneous coronary intervention; Coronary artery bypass grafting; Left ventricular ejection fraction

1. Introduction

Sudden cardiac death (SCD) is reported to be the cause of more than half of all cardiac deaths, and ventricular arrhythmia is believed to be the most common cause of SCD [1]. The purpose of the present study was to evaluate the incidence and the relative value of both reduced left ventricular ejection fraction (LVEF) and multiple comorbidities for estimating the precise risk stratification of SCD in patients after coronary revascularization.

2. Patients and methods

Considerable data have been added to the coronary revascularization demonstrating outcome study in Kyoto (CREDO-Kyoto) registry regarding potential risk factors and outcome of 9877 consecutive patients who underwent first elective percutaneous coronary intervention (PCI; $n=6878$) and then coronary artery bypass grafting (CABG; $n=2999$) at 30 institutions in Japan between 200 and 2002. The description of the study design and protocol has been published previously [2]. To determine the clinical predictors of SCD in patients after PCI and CABG, we performed a

Abbreviations: SCD, sudden cardiac death; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease.

☆ All authors have read and approved the manuscript. The authors have no conflict of interests to declare.

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Table 1
Patient and disease characteristics and univariate relationships with sudden cardiac death by Cox proportional-hazards model

	Patients with characteristics				Univariate relationships with SCD		
	Overall (n=9756)		Victims of SCD (n=140)				
Variable	n	%	n	%	Hazard ratio	95% CI	P-value
Left ventricular dysfunction (LVEF≤30%)	261	3.0%	17	12.1%	2.35	1.79–3.00	<0.0001
Dialysis	408	4.1%	29	20.7%	2.82	2.28–3.44	<0.0001
COPD	240	2.4%	13	9.3%	2.12	1.55–2.76	<0.0001
Congestive heart failure	1214	12.5%	50	35.7%	2.01	1.75–2.48	<0.0001
Chronic renal disease	1401	14.4%	92	65.7%	1.84	1.54–2.21	<0.0001
Diabetes with insulin therapy	820	8.3%	27	19.3%	1.70	1.37–2.07	<0.0001
Anemia	2536	26.3%	61	43.6%	1.56	1.32–1.85	<0.0001
Chronic total occlusion of coronary artery	3023	30.6%	67	47.9%	1.47	1.25–1.74	<0.0001
Peripheral artery disease	1141	11.6%	31	22.1%	1.53	1.24–1.85	0.0001
Body mass index*	23.6±3.3		22.7±3.3		0.90	0.86–0.95	0.0002
Triple vessel disease	3205	32.5%	62	44.3%	1.30	1.10–1.53	0.0003
Having PCI	6878	69.6%	84	60.0%	0.81	0.68–0.96	0.0160
Age#	67.3±9.9		68.7±9.9		1.02	1.01–1.04	0.0371
Chronic atrial fibrillation	233	2.4%	7	5.0%	1.54	1.01–2.17	0.0490
Female gender	2897	29.3%	33	23.6%	0.86	0.70–1.03	0.1084
Malignancy	703	7.1%	14	10.0%	1.27	0.94–1.65	0.1086
Hypertension	6811	69.0%	102	72.9%	1.09	0.91–1.33	0.3409
Emergency procedure	544	5.5%	9	6.4%	1.13	0.78–1.54	0.4880
Cerebrovascular disease	1643	16.7%	25	17.9%	1.07	0.85–1.32	0.5509
Left main coronary artery disease	956	9.7%	15	10.7%	1.06	0.79–1.36	0.6831
Current smoker status	2732	28.2%	37	26.4%	0.98	0.81–1.18	0.8234
Diabetes without insulin therapy	2942	29.8%	44	31.4%	1.02	0.85–1.21	0.8338
Proximal left anterior descending coronary artery disease	7090	71.8%	101	72.1%	1.01	0.84–1.22	0.9352

*Hazard ratio for 1 increase in body mass index; # Hazard ratio for 1 increase in age.
SCD=sudden cardiac death; CI=confidential index; LVEF=left ventricular ejection fraction; COPD=chronic obstructive pulmonary disease.

post-hoc analysis of SCD in 9756 consecutive patients who survived first elective PCI (n=6846) and CABG (n=2910) from long-term result of this registry.

SCD was explicitly defined as death that occurred suddenly and unexpectedly in patients whose condition was otherwise stable. SCD was further classified as witnessed death (with or without the incidence of arrhythmia) and unwitnessed death if the patient had been examined within 24 h before death but no premonitory heart failure, myocardial infarction, or any other clear cause of death was suspected.

Survival curves were analyzed using the Kaplan–Meier method and compared using the log-rank statistic and to determine the baseline risk factors for the incidence of SCD, we developed Cox proportional hazard models for the 23 potential variables (Table 1). Further, we developed multivariate Cox proportional hazard models that controlled for significant risk factors of SCD. The variables for which p-values were less than 0.05 in univariate analyses and proportional assumptions were generally fair were included

Table 2
In-hospital and long-term clinical outcomes

In-hospital clinical outcomes	N	%
In-hospital Q wave myocardial infarction	92	0.9%
In-hospital death	121	1.2%
Long-term clinical outcomes	N	%
Average follow up period (days)	1285±469	
Death from any cause	906	9.4%
Cardiovascular death	517	5.4%
Cardiac death	376	3.9%
SCD	140	1.5%

SCD=sudden cardiac death.

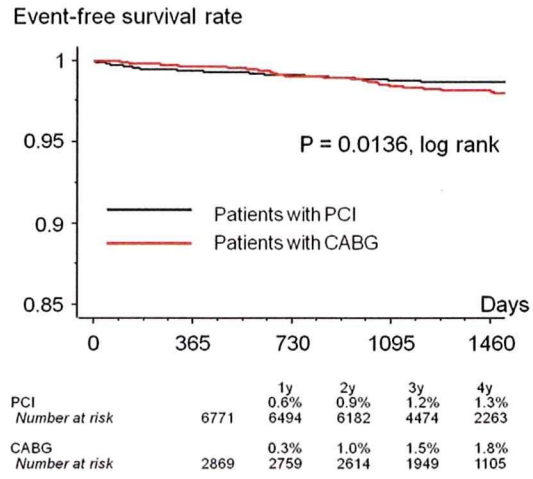

Fig. 1. Unadjusted Kaplan–Meier event-free survival curves for sudden cardiac death in patients after PCI or CABG.

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Table 3
Multivariate relationships with sudden cardiac death by Cox proportional-hazards model

Variable	Hazard ratio	95% CI	*P*-value
Dialysis	2.51	1.90–3.30	<0.0001
COPD	2.04	1.48–2.70	0.0001
Congestive heart failure	1.63	1.32–1.99	<0.0001
Left ventricular dysfunction (LVEF≤30%)	1.55	1.16–2.03	0.0041
Chronic total occlusion of coronary artery	1.38	1.14–1.67	0.0009
Diabetes with insulin therapy	1.33	1.03–1.67	0.0267
Chronic renal disease	1.29	1.01–1.65	0.0386
Peripheral artery disease	1.27	1.01–1.58	0.0395
Chronic atrial fibrillation	1.53	0.99–2.17	0.0552
Triple vessel disease	1.06	0.87–1.33	0.5557
Undergoing PCI	1.09	0.89–1.33	0.4239
Age[#]	1.02	1.00–1.04	0.1221
Body mass index *	0.99	0.93–1.19	0.7392
Anemia	0.97	0.78–1.99	0.7467

[#]Hazard ratio for 1 increase in age; *Hazard ratio for 1 increase in body mass index.
CI=confidential index; LVEF=left ventricular ejection fraction; PCI=percutaneous coronary intervention.

in the multivariate analysis. All analyses were performed using JUMP software version 6.0.3 (SAS, Cary, NC).

3. Results

Baseline clinical characteristics are listed in Table 1. The long-term follow-up (median follow-up period=42.8 months) for 98% patients was completed at 1 year, and that for 95% at 2 years. In-hospital and long-term clinical outcomes are listed in Table 2. At 3 years, the unadjusted survival rate was 92.1% and the rates of freedom from cardiovascular death, cardiac death, and SCD were 95.3%, 96.5%, and 98.7%, respectively. Among the total patients studied, 265 patients (2.7%) suffered acute myocardial infarction and 468 patients (4.8%) suffered stroke. In addition, 4 patients received implantable cardioverter–defibrillator therapy and 4 patients underwent cardiac resynchronization therapy.

The incidence of SCD was significantly higher in patients with CABG ($p=0.0136$, log rank). The rates of incidence of SCD were 0.6%, 0.9%, and 1.2% in patients with PCI and 0.3%, 1.0%, and 1.5% in patients with CABG at 1, 2, and 3 years, respectively (Fig. 1).

Univariate analysis revealed that dialysis, congestive heart failure, COPD, left ventricular dysfunction (LVEF≤30%), chronic total occlusion of coronary artery, diabetes with insulin therapy, chronic atrial fibrillation, peripheral artery disease, chronic renal disease, age, triple vessel disease, body mass index, and anemia were associated with higher incidence of SCD, and that PCI therapy provided protection against SCD. Among those who died of SCD, only 17 patients (12.1%) suffered from left ventricular dysfunction (LVEF≤30%) (Table 1). Multivariate analyses indicated that dialysis (hazard ratio=2.51), COPD (hazard ratio=2.04), congestive heart failure (hazard ratio=1.63), left ventricular dysfunction (LVEF≤30%) (hazard ratio=1.55), chronic total occlusion of coronary artery (hazard ratio=1.38), diabetes with insulin therapy (hazard ratio=1.33), chronic renal disease (hazard ratio=1.29), and peripheral artery disease (hazard ratio=1.27) were independent predictors of SCD after PCI and CABG (Table 3). The multivariate analyses revealed that the method of revascularization had no influence on the incidence of SCD (Table 3).

4. Discussion

It has not been examined well whether coronary revascularization and the method of revascularization have any influence on the incidence of SCD in patients with ischemic heart disease; however, the relatively low incidence of SCD observed in this study (the rates of SCD were 0.5%, 0.9%, and 1.3% at 1, 2, and 3 years) may be attributed to coronary revascularization. A bypass angioplasty revascularization investigation (BARI) trial revealed that CABG decreased the risk of SCD to a significantly greater extent than PCI in patients with multivessel disease [3]; however, this study demonstrated in the bare-metal stent era the method of revascularization had no influence on the incidence of SCD.

Drug-eluting stents are designed to reduce neointimal formation, thus leading to lower restenosis rates. However, the action of the drugs will delay endothelialization and healing and possibly induce hypersensitivity to the drug or polymer and lead to an increased risk of thrombosis [4,5], which may induce the incidence of SCD and further study may be needed which is focused on the incidence of SCD after coronary revascularization in drug-eluting stents era.

Many recent trials focusing on LVEF in patients with ischemic heart disease [6–14]. In this study, left ventricular dysfunction was demonstrated to be a significant predictor of SCD, only 12.1% patients with SCD had left ventricular dysfunction. From the multivariate analysis, the adjusted hazard ratio of left ventricular dysfunction was only 1.55, which is smaller than that observed for dialysis (adjusted hazard ratio=2.51), COPD (adjusted hazard ratio=2.04), and congestive heart failure (adjusted hazard ratio=1.63). This indicated that the LVEF before revascularization had only limited value for predicting the risk of SCD.

5. Conclusion

This study demonstrated that the method of revascularization had no influence on the incidence of SCD, and the adjusted hazard ratio of reduced LVEF was smaller than that observed in dialysis, chronic obstructive pulmonary disease, and congestive heart failure in this study, which indicated that the risk of SCD depends on multiple variables in addition to LVEF.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [15].

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Circ J 2009; **73:** 145–151

Efficacy of Abciximab for Patients Undergoing Balloon Angioplasty

—— Data From Japanese Evaluation of c7E3 Fab for Elective and Primary PCI Organization in Randomized Trial (JEPPORT) ——

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Background The efficacy and safety of abciximab were investigated in Japanese patients undergoing percutaneous coronary intervention (PCI) for acute myocardial infarction (MI) or unstable angina.

Methods and Results The 973 patients were randomized into 3 groups: the low-dose group (L group) received bolus injection of 0.20 mg/kg followed by 12-h infusion; the high-dose group (H group) received bolus injection of 0.25 mg/kg followed by 12-h infusion; the placebo group (P group) received bolus and infusion of placebo. The incidence of the primary endpoint (30-day post-PCI coronary events: death, MI or urgent revascularization) was 3.6%, 1.6%, and 4.1% in the P, L, and H groups, respectively, with no significant difference between the P and L groups (P=0.104) or between the P and H groups (P=0.772). The incidence of bleeding tended to increase in a dose-dependent manner.

Conclusion No significant difference in the incidence of coronary events was found between the placebo and abciximab groups, so the efficacy of abciximab in preventing post-PCI coronary events in Japanese patients was not confirmed. (*Circ J* 2009; **73:** 145–151)

Key Words: Abciximab; Angioplasty; GPIIb/IIIa; Myocardial infarction; Unstable angina

Percutaneous coronary intervention (PCI) is a revascularization procedure for ischemic heart disease and, as techniques and devices have improved, the usefulness of elective PCI, not only for stable angina, but also for acute myocardial infarction (MI) and unstable angina (UA), has been recognized. However, post-PCI coronary events, such as recurrence of ischemic symptoms requiring urgent revascularization and/or MI occasionally resulting in death, are unsolved therapeutic problems[1–7] occuring in approximately 2% of low-risk patients and 10–20% of high-risk patients, and despite antiplatelet and antithrombotic therapies, outcomes are not necessarily satisfactory[5–11]

Abciximab is a glycoprotein (GP) IIb/IIIa inhibitor of human–mouse monoclonal antibody (c7E3 Fab). Large-scale clinical studies, including EPIC (2,099 cases)[8] EPILOG (2,792 cases)[9] CAPTURE (1,265 cases),[10] and EPISTENT (2,399 cases),[11] have consistently demonstrated its efficacy and the use of abciximab during PCI is recommended in the ACC/AHA guidelines[12,13] During the present study, abciximab had not been approved by the Ministry of Health, Labour and Welfare for use in Japan, although it has been approved in more than 50 countries for the prevention of acute cardiac ischemic complications in patients undergoing PCI. We evaluated the efficacy and safety of abciximab in a double-blind, placebo-controlled, comparative study of Japanese patients undergoing PCI.

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Methods

Patient Population

We used a placebo control by double-blind comparative method based on results from evaluation and observation for 6 months after starting abciximab therapy. The study was conducted in patients undergoing PCI for acute MI or UA. MI was defined as an attack presenting within 12 h of the onset of chest pain lasting ≥20 min and accompanied by ST-segment elevation ≥0.1 mV in ≥2 leads or occurrence of Q waves 0.04 s in width and/or 0.25% of R waves in depth. UA was defined as either (1) rest angina (ie, angina or rest and effort angina unresponsive to medication and accompanied by an ischemic ST-segment abnormality or T-wave abnormality on EKG) or (2) post-infarction angina (ie, occurring within 7 days after a documented episode of MI and accompanied by an ischemic ST-segment abnormality or T-wave abnormality on EKG).

Midway through this study, overseas authorities stipulated that the approved intravenous drip infusion dose of abciximab be adjusted according to body weight, so we temporarily discontinued the study for safety reasons and resumed it after making the changes to the dosage. There-

fore, "Study #01" ran until the discontinuation and "Study #02" after the resumption.

The exclusion criteria were: (1) ≥75 years old in Study #02 (no upper limit for #01); (2) >100 kg of body weight in Study #02 (no upper limit for #01); (3) scheduled for primary stent placement, directional coronary atherectomy or rotablator; (4) history of thrombocytopenia; (5) bleeding symptoms or bleeding diathesis; (6) undergone surgery in the previous 6 weeks; (7) cerebrovascular disorder or a history of such in the previous 2 years; (8) ≥50% stenosis in the left main trunk of the coronary artery; (9) 3-vessel disease; (10) uncontrollable hypertension and pulmonary hypertension; and (11) cardiogenic shock requiring cardiopulmonary resuscitation.

The study was approved by the institutional review board at each study site and written informed consent was given by either the patient or a representative before starting the protocol.

Study Design

After initial coronary angiography had identified the culprit lesion, enrolled subjects were randomly assigned into 3 groups according to the dosage of abciximab: the low-dose group (L group) received an intravenous bolus injection of 0.20 mg/kg followed by 12-h continuous intravenous drip infusion of 10 μg/min in Study #01 or 0.125 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in Study #02; the high-dose group (H group) received an intravenous bolus injection of 0.25 mg/kg followed by 12-h continuous intravenous drip infusion using the same dose as in the L group; placebo group (P group) received bolus injection and 12-h continuous drip infusion of the placebo. Coronary angiography was performed 10 min after the bolus injection, before starting the PCI procedure.

Heparin (initial dose: 100 units/kg in Study #01; 70 units/kg in Study #02) and aspirin (≤162 mg/day) were used concomitantly with abciximab, but the following drugs was prohibited during the 6 months from the start of the investigation: thrombolytic drugs, antiplatelet drugs other than aspirin (ticlopidine was permitted in bailout stent placement cases), anticoagulant drugs other than heparin, PGE_1 and its derivatives, dextran, and low-molecular-weight dextran.

PCI Procedure and Criteria for the Use of Bailout Stent

PCI (balloon angioplasty) was performed by the standard procedure of each institution. Bailout stenting was permitted if (1) there was markedly delayed contrast flow, defined as Thrombolysis In Myocardial Infarction (TIMI) flow grade ≤2;[14] or (2) a major morphological problem, such as dissection, occurred.

Efficacy Endpoints

The primary efficacy endpoint was the incidence of major coronary events within 30 days after randomization. Major coronary events were defined as death, MI and/or urgent revascularization for recurrence of ischemia. The secondary endpoint was the incidence of major coronary events during the 6 months post-treatment. MI as a coronary event was defined as follows.

(1) MI during the index hospitalization was defined separately according to the initial presentation and duration from the onset of chest pain. (A) In a patient enrolled in the setting of acute MI, MI within 24 h was adjudicated when presenting with subjective symptoms such as chest pain and ≥0.1 mV increase in the ST-segment elevation in ≥2 leads, lasting for ≥30 min. (B) MI after 24 h in patients enrolled in the setting of acute MI and MI in patients enrolled in the setting of UA were regarded as being present when at least 1 of the following was documented: (i) creatine kinase MB isoenzyme (CK-MB) or creatine kinase (CK) value increased by ≥50% compared with the closest trough and peaking at ≥3-fold the upper limit of normal. In cases that did not have a trough, the baseline values are regarded as such; (ii) Q-wave newly detected in leads at ≥2 sites, with a width ≥0.04 s, and/or depth ≥25% of the R-wave.

(2) MI after hospital discharge was adjudicated when at least 1 of the following occurred: (i) CK-MB or CK value ≥twice the upper limit of normal; (ii) new Q-wave with a width ≥0.04 s, and/or depth ≥25% of the R-wave in ≥2 leads.

Secondary Endpoints With Image Analysis

Efficacy was also assessed by secondary endpoints with image analysis (based on quantitative coronary angiography, QCA). Participation was not mandatory. Image analysis was performed at the core image analysis laboratory and assessed by the Efficacy Review Committee to maintain consistency in both the evaluation and accuracy of measurement. Restenosis was classified as ≥50% diameter stenosis at the treated site 6 months post-PCI.

Based on the angiographic findings, the efficacy for prevention of thrombus formation was evaluated from 1 to 4, as described below. Intracoronary thrombus was defined as an irregular filling defect, outlined and/or stained by contrast medium and in the absence of calcification within the filling defect, or by the presence of a mobile irregular filling defect.

1. Very effective: (i) improvement in blood flow by ≥2 TIMI grades in subjects with TIMI grade 0 or 1 flow or (ii) complete disappearance of an apparent thrombus in subjects with TIMI grade 2 or 3 flow.
2. Effective: (i) improvement in blood flow by 1 TIMI grade in subjects with TIMI grade 0–2 flow or (ii) reduction in the size of an apparent thrombus in subjects with TIMI grade 3 flow, or (iii) improvement (≥10% decrease) in % diameter stenosis by QCA in subjects with no change in TIMI grade.
3. Ineffective: (i) no change in blood flow in subjects with TIMI grade 0–3 flow or (ii) no change in the size of an apparent thrombus in subjects with TIMI grade 0–3 flow, or no improvement in blood flow in subjects with TIMI grade 0–3 flow without an apparent thrombus; (iii) aggravation (≥10% increase) of % diameter stenosis by QCA in subjects with no change in TIMI grade.
4. Aggravated: (i) decrease in blood flow in subjects who had TIMI grade 0–3 flow, or (ii) enlargement of an apparent thrombus in subjects with TIMI grade 0–3 flow.

Safety Endpoints

To evaluate safety, bleeding symptoms and thrombocytopenia were assessed within 6 months in Study #01 and within 30 days in Study #02. The severity of bleeding events was judged according to the TIMI bleeding criteria![15]

Platelet count was measured before the investigational treatment as baseline and at 2–3 h, 8–12 h, 24 h, 2 weeks, 30 days, and 6 months after the start of the investigational treatment. Thrombocytopenia was defined as platelet count <100,000/mm^3 and a decrease by ≥25% from the baseline.

Statistical Analysis

All significance levels were 2-sided and set at 5%. The combined results were used in the efficacy analysis of post-

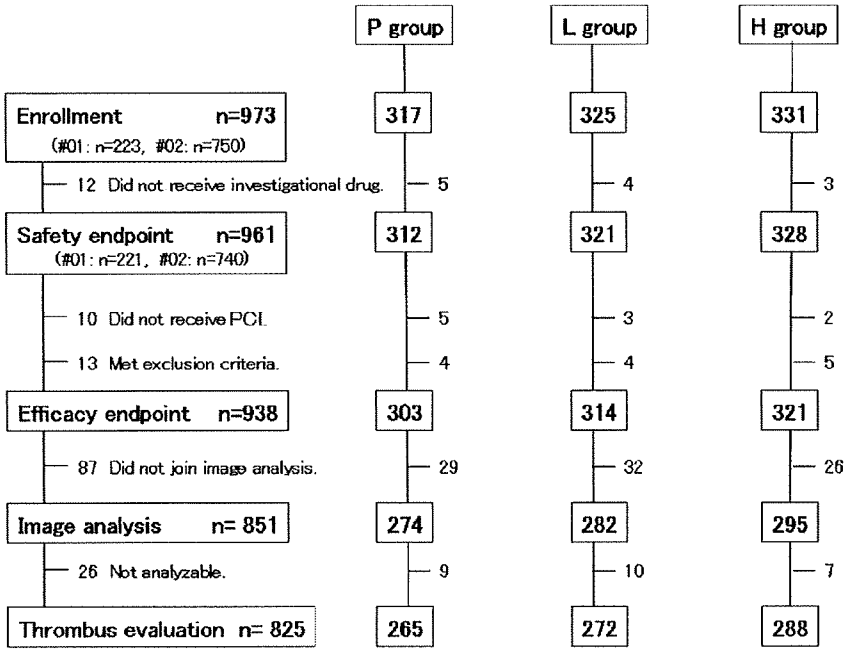

Fig 1. Flow chart of the study population with the reasons for exclusion, according to treatment group. H, high-dose; L, low-dose; P, placebo; PCI, percutaneous coronary intervention.

Table 1 Baseline Characteristics of the Patients According to Treatment Group

	P group (n=303)	*L group (n=314)*	*H group (n=321)*
Acute MI	*233 (77%)*	*237 (76%)*	*250 (78%)*
Unstable angina	*70 (23%)*	*77 (25%)*	*71 (22%)*
Rest angina	*20*	*21*	*20*
Rest and effort angina	*32*	*39*	*30*
Post-infarction angina	*16*	*17*	*21*
Male	*251 (83%)*	*258 (82%)*	*252 (79%)*
Age (years, mean±SD)	*60.2±9.5*	*61.1±9.4*	*60.8±10.1*
Range	*32–85*	*32–87*	*29–84*
Diabetes	*91 (30%)*	*96 (32%)*	*101 (31%)*
Hypertension	*154 (51%)*	*169 (54%)*	*164 (51%)*
Hyperlipidemia	*145 (48%)*	*136 (44%)*	*141 (44%)*
Smoking	*202 (67%)*	*187 (60%)*	*183 (57%)*
Obesity	*33 (11%)*	*42 (13%)*	*55 (17%)*
Family history of ischemic disease	*48 (16%)*	*55 (18%)*	*56 (17%)*
Bailout stent use	*77 (25%)*	*74 (23%)*	*83 (26%)*

P, placebo; L, low-dose; H, high-dose; MI, myocardial infarction.

PCI coronary events. Depending on the characteristics of the background factors, the chi-square test (nominal scale), Mantel test (ordered scale) or Kruskal–Wallis test (continuous scale) was used. The primary endpoint was analyzed as a time-to-event variable, and the cumulative incidence rate was determined by the Kaplan–Meier method. Comparisons of incidence among the groups were performed using the log-rank test, which was used for the main analysis. Separate results from Studies #01 and #02 were used for the safety analysis.

Target Sample Size In the EPIC trial[8] the incidence of postoperative major coronary events within 30 days after PCI was 13.1% in UA patients receiving placebo (n=153), 3.8% in UA patients receiving abciximab continuous drip infusion (n=156), 26.1% in acute MI patients receiving placebo (n=23), and 4.5% in acute MI patients receiving abciximab continuous drip infusion (n=22). Although it was expected that drug efficacy would be more clearly observed in patients with acute MI, the data obtained from the UA patients were used to determine the target sample size for the present study in order to increase the power of statistical analysis. Based on the EPIC data, the expected incidence of postoperative major coronary events in the P group was 15%, and that in the H group was 7.5% (ie, 50% less than that in the P group). When the incidence was compared between the P and H groups, assuming scores (contrast) of −1, 0, and 1 for the P, L, and H groups, respectively, it was determined that a sample size of 300 in each group provided a statistical power of 79.5% at α=0.05 (2-sided), based on the binomial distribution of difference in the incidence.

Results

Study Population

From May to November 1997, 223 subjects were enrolled in Study #01, and from October 1998 to April 2000, 750 subjects were enrolled in Study #02 from 89 study sites (Appendix 1). Of the 973 enrolled subjects, 961 received the investigational drug and were used for safety endpoint analysis. The flowchart of the study population with the reasons for exclusion is shown in **Fig 1**. Data from 938 subjects (303 in the P group, 314 in the L group, and 321 in the

Table 2 Efficacy Endpoint

Endpoint	7 days				30 days		
	P group (n=303)	L group (n=314)	H group (n=321)	L+H group (n=635)	P group (n=303)	L group (n=314)	H group (n=321)
Death + MI + Urgent revascularization	10 (3.3%)	4 (1.3%)	7 (2.2%)	11 (1.7%)	11 (3.6%)	5 (1.6%)	13 (4.1%)
P		0.083	0.408	0.125		0.104	0.772
Death	0 (0.0%)	1 (0.3%)	1 (0.3%)	2 (0.3%)	0 (0.0%)	1 (0.3%)	1 (0.3%)
MI	9 (3.0%)	3 (1.0%)	6 (1.9%)	9 (1.4%)	9 (3.0%)	3 (1.0%)	9 (2.8%)
Urgent revascularization	2 (0.7%)	0 (0.0%)	2 (0.6%)	2 (0.3%)	3 (1.0%)	1 (0.3%)	8 (2.5%)

P values (log-rank test): P group vs L group, P group vs H group, P group vs L+H group.
Abbreviations see in Table 1.

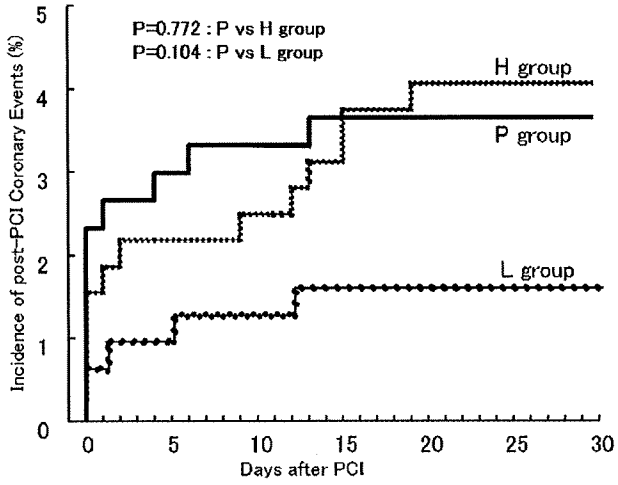

Fig 2. Kaplan-Meier plot of 30-day cumulative incidence of post-PCI coronary events. Abbreviations see in Fig 1.

H group) were used for the efficacy analysis. The image analysis subset comprised 851 subjects, and 825 cases of thrombi were evaluated at the coronary angiogram image analysis laboratory.

The baseline characteristics of study population are shown in **Table 1**. There was no significant difference among the groups in their baseline characteristics.

Efficacy Endpoint

The cumulative incidence rates of post-PCI coronary events during 30 days were 3.6% in the P group, 1.6% in the L group, and 4.1% in the H group, with no significant difference between the P and L groups (P=0.104) or between the P and H groups (P=0.772; **Table 2**). The Kaplan–Meier plot of the 30-day cumulative incidence rates is shown in **Fig 2**. The cumulative incidence rates of post-PCI coronary events during 6 months were 14.1% in the P group, 15.0% in the L group, and 15.0% in the H group, with no significant difference between the P and L or H groups.

Secondary Endpoints With Image Analysis

The angiographic restenosis rate was 32.9%, 34.9%, and 37.1% in the P, L, and H groups, respectively, with no significant differences between the P and L or H groups. The effectiveness (very effective plus effective) for prevention of thrombus formation was 13.9%, 12.9%, and 19.4% in the P, L, and H groups, respectively, (P vs L: P= 0.664, P vs H: P=0.028; **Table 3**).

Safety Endpoint

Table 4 shows the incidence of bleeding complications. The incidence of bleeding complications (minor or major) increased dose-dependently, with a significant difference between the P and H groups (Study #01: P=0.010; Study #02: P=0.020). Major bleeding occurred in 2 cases (2.5%) in the H group in Study #01 and in 1 case (0.4%) each in the P and H groups in Study #02, without any significant difference among the groups. There was no major bleeding in the L group.

The incidence of thrombocytopenia, defined as ≥25% decrease from baseline count and platelet count <100,000/mm^3, was 1.4% in the P group, 8.8% in the L group, and 10.4% in the H group (P=0.035) in Study #01; and 1.7% in the P group, 6.6% in the L group (P=0.010), and 8.3% in the H group (P=0.001) in Study #02 (**Table 5**). The incidence increased dose-dependently, and there was a significant difference between the placebo and active treatment groups. As for the incidence of thrombocytopenia with ≥25% decrease from baseline count and platelet count <50,000/mm^3, only 1 case (1.5%) in the L group and 4 cases (5.2%) in the H group in Study #01, and 2 (0.8%) each in the L and H groups in Study #02 were reported, with no significant difference among the groups.

Exploratory Analysis

The cumulative incidence rate of post-PCI coronary events observed during 7 days after PCI (**Table 2**) was 3.3%, 1.3%, 2.2%, and 1.7% in the P, L, H, and abciximab (L plus H) groups, respectively. Although no significant difference was observed between the P and L or H or abciximab groups, event reduction rate during this period in the abcix-

Table 3 Efficacy of Abciximab Against Thrombus

	Very effective	Effective	Ineffective	Aggravated	Effectiveness rate (95%CI)	P value
P group (n=265)	12 (4.5%)	25 (9.4%)	218 (82.3%)	10 (3.8%)	13.9% (10.02–18.73)	
L group (n=272)	7 (2.6%)	28 (10.3%)	230 (84.6%)	7 (2.6%)	12.9% (9.13–17.44)	0.664
H group (n=288)	14 (4.9%)	42 (14.6%)	230 (79.9%)	2 (0.7%)	19.4% (15.04–24.49)	0.028

P values (Mantel test): P group vs L group, P group vs H group. Effectiveness = very effective + effective.
CI, confidence interval. Other abbreviations see in Table 1.

Table 4 Incidence of Bleeding Complications During the Study Periods

	Study #01 (6 months)			Study #02 (30 days)		
	P group (n=71)	L group (n=71)	H group (n=79)	P group (n=241)	L group (n=250)	H group (n=249)
Major+minor bleeding	1 (1.4%)	4 (5.6%) (P=0.366)	10 (12.7%) (P=0.010)	6 (2.5%)	11 (4.4%) (P=0.325)	18 (7.2%) (P=0.020)
Major bleeding	0	0	2 (2.5%)	1 (0.4%)	0	1 (0.4%)
Minor bleeding	1 (1.4%)	4 (5.6%)	8 (10.1%)	5 (2.1%)	11 (4.4%)	17 (6.8%)
Site of bleeding						
Inguinal	2 (2.8%)	3 (4.2%)	8 (10.1%)	4 (1.7%)	11 (4.4%)	13 (5.2%)
Puncture	0	0	2 (2.5%)	4 (1.7%)	9 (3.6%)	11 (4.4%)
Urogenital	2 (2.8%)	4 (5.6%)	6 (7.6%)	4 (1.7%)	7 (2.8%)	10 (4.0%)
Gingival	0	4 (5.6%)	5 (6.3%)	0	2 (0.8%)	11 (4.4%)
Hematoma	0	3 (4.2%)	4 (5.1%)	7 (2.9%)	9 (3.6%)	15 (6.0%)

The severity of bleeding was judged according to the TIMI bleeding criteria[18]
P values: P group vs L group, P group vs H group.
TIMI, Thrombolysis In Myocardial Infarction. Other abbreviations see in Table 1

Table 5 Incidence of Thrombocytopenia During the Study Periods

Platelet count, /mm³	Study #01 (6 months)			Study #02 (30 days)		
	P group (n=70)	L group (n=68)	H group (n=77)	P group (n=240)	L group (n=243)	H group (n=241)
<50,000	0	1 (1.5%) (P=0.493)	4 (5.2%) (P=0.122)	0	2 (0.8%) (P=0.499)	2 (0.8%) (P=0.499)
≥50,000 <100,000	1 (1.4%)	5 (7.4%)	4 (5.2%)	4 (1.7%)	14 (5.8%)	18 (7.5%)
<100,000	1 (1.4%)	6 (8.8%) (P=0.061)	8 (10.4%) (P=0.035)	4 (1.7%)	16 (6.6%) (P=0.010)	20 (8.3%) (P=0.001)

P values: P group vs L group, P group vs H group. Thrombocytopenia defined as ≥25% decrease from baseline count and platelet count <100,000/mm³. Abbreviations see in Table 1

imab group was 48.5%.

Discussion

Primary Efficacy Endpoint

The present study was the first large-scale clinical trial to be conducted in Japan to investigate the efficacy and safety of abciximab for prevention of post-PCI coronary events. A number of clinical trials[8–11,16–19] have revealed positive effects of GPIIb/IIIa inhibitors in patients with acute coronary syndromes undergoing PCI, and the outcomes of the present study are different from those obtained in countries other than Japan.

At the time of this study, designed with a target of 300 patients in each group, the expected incidence of postoperative events in the P group was 15%, and that in the H group was 7.5%, based on data from the EPIC trial[8] Because the actual incidence of coronary events was much lower than expected, the statistical power was considered insufficient for verification of the efficacy of abciximab. In this study, patients with acute MI accounted for approximately 75% of the study patients, and only 2 patients died (0.21%), suggesting that most of the recruited patients had relatively mild disease. Thus, it is considered that these patients did not represent the patient population requiring treatment with abciximab, because elderly patients (≥75 years of age in Study #02) and patients with 3-vessel disease and cardiogenic shock, which are known risk factors for postoperative coronary events[1–4,20] were excluded. Further research is required to identify the patient population actually requiring treatment with abciximab, and clinical trials with this population should be performed in order to evaluate the efficacy of abciximab in Japan.

In the EPIC trial[8] conducted in the era of plain old balloon angioplasty (POBA), bailout stent implantation was regarded as a post-PCI event and in their incidence of stent implantation was 1.7%, 0.6%, and 0.6% in the P, low-dose (0.25 mg/kg bolus), and high-dose (0.25 mg/kg bolus followed by 12-h drip infusion) group, respectively. In contrast, in the present study, conducted during the transition from the POBA era to the stent era, bailout stent implantation was performed in approximately 25% of patients and was not considered to be a post-PCI coronary event. It is thought that bailout stent implantation can prevent reocclusion and potentially reduce the incidence of post-PCI coronary events?[21,22] Thus, there is a possibility that the conceptual difference in coronary stenting, because of changes in the standard of care treatment, contributed to the reduced overall incidence of post-PCI coronary events and affected the results of this study.

It has been suggested that Asians may have different prognoses for acute coronary syndrome, thrombogenicity and bleeding tendency compared with Caucasians. Nakamura et al[23] reported prognoses following an acute coronary event in Japanese and North American patients who were prospectively enrolled in a multicenter study. Their results indicated a more favorable outcome in Japanese patients than in North American patients, even after adjusting for differences in clinical variables. The stent thrombosis rate in Japanese patients[24] was much lower than that reported in Western patients?[25,26] and stent thrombosis is known to be related to platelet activation and aggregation?[27] The CRUSADE study[28] compared 1,071 Asian and 72,513 non-Asian white patients with non-ST elevation MI.

Although in-hospital mortality and reinfarction rates were similar between groups, rates of major bleeding (13.4% vs 9.4%, P<0.0001) and red blood cell transfusion (9.6% vs 6.6%, P=0.0005) were significantly higher in the Asian population, which suggests that Asians, including Japanese, have an ethnic variability in antithrombotic susceptibility and that may have affected the results of the present study.

Secondary Endpoints With Image Analysis

In the present study, the angiographic findings indicated that the effectiveness against thrombus formation was 13.9% and 19.4% in the P and H groups, respectively, with a statistically significant difference (P=0.028). Regarding the effects of abciximab on thrombus formation during the first 10 min after administration, Gold et al reported that coronary flow increased by at least 1 TIMI grade in 85% and reached TIMI grade 2 or 3 in 54% in patients with acute MI.[29] A study of abciximab used with thrombolytic agents for thrombolysis has also reported that the proportion of patients who achieved TIMI grade 3 flow at 60–90 min after the start of treatment was significantly greater in the group receiving abciximab than in the group not receiving abciximab.[30] Those findings, together with our results, suggest that abciximab can separate and break down thrombi.

Safety Evaluation

The incidences of hemorrhagic complications and thrombocytopenia were higher in the abciximab-treated groups than in the placebo group. In Study #02, the protocol was changed to prevent hemorrhagic complications and serious thrombocytopenia (eg, by establishing the upper age limit, adding and modifying exclusion criteria, adjusting the dose for intravenous drip infusion according to body weight, and reducing the initial dose of heparin). It was strongly suggested that these changes in the study design would significantly decrease the incidences of hemorrhagic events and serious thrombocytopenia associated with abciximab. In Studies #01 and #02, the incidences of minor and major bleeding tended to increase dose-dependently. Although significant differences were found between the P and H groups, no significant difference was found between the P and L groups. In addition, there was no major bleeding in the L group. Therefore, we consider that for Japanese patients the low-dose abciximab regimen is safer than the high-dose regimen.

Exploratory Analysis

Because the effect of abciximab appears most clearly during the 7-day postoperative period,[8,9] we analyzed the incidence of coronary events during the 7 days after PCI. Although no significant difference was observed, the events reduction rate of 48.5% in the abciximab-treated group during this period was similar to that observed in large-scale foreign clinical trials (EPIC trial:[8] 32.8%; EPILOG trial:[9] 55.2%), suggesting the efficacy of abciximab in preventing post-PCI coronary events in Japanese patients.

Study Limitations

The timeliness in publication of the study results requires mention. In the 8 years since the enrollment and follow-up of patients was completed for the present study, progress had been made in the fields of interventional cardiology and antithrombotic treatment, and so the outcomes of this study may no longer reflect current clinical practice. However, the International Committee of Medical Journal Editors (ICMJE) states the importance of publicizing negative data from randomized clinical trials.[31] ICMJE also emphasizes that trials should be registered at the time they are set up. The present trial was designed and started before the registration system was established. Although the results are inconclusive and lack timeliness, this study has been the only clinical trial of abciximab in Japanese patients.

Conclusion

Administration of abciximab in Japanese patients with acute coronary syndrome undergoing PCI had no efficacy in reducing major coronary events, with a significant increase in both bleeding and thrombocytopenia.

Disclosure

Authors have no relationships or conflicts.

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Appendix 1

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