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Short-duration triple antithrombotic therapy for atrial fibrillation patients who require coronary stenting: results of the SAFE-A study

Tomoya Hoshi[1]*, MD; Akira Sato[1], MD; Daigo Hiraya[1], MD; Hiroaki Watabe[1], MD; Noriyuki Takeyasu[2], MD; Akihiko Nogami[1], MD; Tomohiro Ohigashi[3], MA; Masahiko Gosho[4], PhD; Masaki Ieda[1], MD; Kazutaka Aonuma[1], MD; for the SAFE-A Investigators

1. Department of Cardiology, Faculty of Medicine, University of Tsukuba, Tsukuba City, Ibaraki, Japan; 2. Department of Cardiology, Ibaraki Prefectural Central Hospital, Ibaraki, Japan; 3. Department of Biostatistics, Tsukuba Clinical Research & Development Organization, University of Tsukuba, Tsukuba City, Ibaraki, Japan; 4. Department of Biostatistics, Faculty of Medicine, University of Tsukuba, Tsukuba City, Ibaraki, Japan

A list of the SAFE-A investigators can be found in Supplementary Appendix 1.

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KEYWORDS

- anticoagulant therapy
- atrial fibrillation
- drug-eluting stent

Abstract

Aims: We aimed to determine whether shortening the duration of $P2Y_{12}$ inhibitor therapy can reduce the risk of bleeding without increasing the risk of major adverse cardiovascular events following coronary stenting in patients with atrial fibrillation (AF).

Methods and results: The SAFE-A is a randomised controlled trial that compared one-month and six-month $P2Y_{12}$ inhibitor therapy, in combination with aspirin and apixaban for patients with AF who require coronary stenting. The primary endpoint was the incidence of any bleeding events, defined as Thrombolysis In Myocardial Infarction major/minor bleeding, bleeding with various Bleeding Academic Research Consortium grades, or bleeding requiring blood transfusion within 12 months after stenting. The study aimed to enrol 600 patients but enrolment was slow. Enrolment was terminated prematurely after enrolling 210 patients (72.7±8.2 years; 81% male). The incidence of the primary endpoint did not differ between the one-month and six-month groups (11.8% vs 16.0%; hazard ratio [HR] 0.70, 95% confidence interval [CI]: 0.33-1.47; p=0.35).

Conclusions: The study evaluated the safety of withdrawing the $P2Y_{12}$ inhibitor from triple antithrombotic prescription one month after coronary stenting. However, enrolment was prematurely terminated because it was slow. Therefore, statistical power was not sufficient to assess the differences in the primary endpoint.

**Corresponding author: Department of Cardiology, Faculty of Medicine, University of Tsukuba, 1-1-1, Tennodai, Tsukuba City, Ibaraki 305-8575, Japan. E-mail: hoshi.tm@md.tsukuba.ac.jp*

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Abbreviations

AF	atrial fibrillation
BARC	Bleeding Academic Research Consortium
CI	confidence interval
CYP2C19	cytochrome P450 2C19
DAPT	dual antiplatelet therapy
HR	hazard ratio
ISTH	International Society on Thrombosis and Haemostasis
NOAC	non-vitamin K oral anticoagulants
PCI	percutaneous coronary intervention
TIMI	Thrombolysis In Myocardial Infarction

Introduction

Approximately 5% to 10% of patients who require coronary stent implantation have an indication for long-term oral anticoagulation to prevent adverse events related to atrial fibrillation (AF)[1,2]. Such patients require triple antithrombotic therapy with aspirin, a $P2Y_{12}$ inhibitor, and an anticoagulant to prevent both stroke and stent thrombosis. However, compared to dual antiplatelet therapy (DAPT), triple antithrombotic therapy is associated with a twofold to threefold increased risk of bleeding complications[3,4]. Therefore, it is of key importance to clarify the risk-benefit profile of triple antithrombotic therapy in such patients.

The WOEST study reported that dual therapy with warfarin and a $P2Y_{12}$ inhibitor was superior to triple therapy with warfarin, a $P2Y_{12}$ inhibitor, and aspirin in terms of the risk of bleeding complications, without compromising protection against major adverse cardiovascular events (MACE) after coronary stent implantation[5]. To date, several randomised controlled trials, including PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS, have demonstrated that non-vitamin K oral anticoagulant (NOAC)-based strategies are superior to warfarin-based triple therapy regarding bleeding event rates[6-8]. For patients with AF who require coronary stenting, the current guidelines recommend that triple therapy with an anticoagulant plus two antiplatelet agents should be administered for one or six months, depending on the individual patient's risk for ischaemia and bleeding[9]. However, the optimal strategy for triple therapy in this patient population remains challenging.

The aim of the present study was to evaluate the safety and effectiveness of short-duration (one-month) $P2Y_{12}$ inhibitor therapy, in combination with aspirin and apixaban, for patients with AF who require percutaneous coronary intervention (PCI) with drug-eluting stent implantation.

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Methods

STUDY DESIGN

The SAFE-A study was a multicentre, prospective, randomised, open-label, clinical trial that compared one-month and six-month $P2Y_{12}$ inhibitor therapy in combination with aspirin and apixaban for patients with AF who require PCI with drug-eluting stent implantation. The major inclusion criteria were non-valvular AF, coronary artery disease indicated for PCI using drug-eluting stents, CHA_2DS_2-VASc score ≥1, and an age of 20 years or older. The major exclusion criteria were stenting of the left main trunk, bifurcation lesion treated with the two-stent technique, advanced chronic kidney disease (creatinine clearance <15 mL/min), and indications for surgery or pulmonary vein isolation. Patients who received any types of second-generation or third-generation drug-eluting stents were included. The design and rationale of the SAFE-A trial, including the full list of inclusion and exclusion criteria, have been reported elsewhere[10]. The study complied with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was approved by the institutional ethics review board of each participating institute, and written informed consent was obtained from all participants. The study was registered in the UMIN Clinical Trial Registry (UMIN000015923).

RANDOMISATION AND TREATMENT

Within 72 hours after PCI, eligible patients were randomised in a 1:1 ratio to receive a $P2Y_{12}$ inhibitor (clopidogrel or prasugrel) for either one month or six months, in combination with both aspirin and apixaban (triple therapy). Randomisation was conducted using an electronic system, stratifying patients by age (≥65 years or <65 years), presence of acute coronary syndrome, and HAS-BLED score (≥3 or <3). Patients received apixaban 5 mg twice daily, which could be reduced to 2.5 mg twice daily if the patient was 80 years or older, had body weight ≤60 kg, or had serum creatinine levels ≥1.5 mg/dL. Either clopidogrel (75 mg/day) or prasugrel (3.75 mg/day) was used as the $P2Y_{12}$ inhibitor at the discretion of the treating physician at the time of enrolment.

ENDPOINTS AND FOLLOW-UP

Patients were evaluated at 1, 3, 6, and 12 months after randomisation to obtain information regarding the occurrence of endpoints, incidence of adverse events, and compliance with the study medication. The primary endpoint of this study was the incidence of any bleeding events within 12 months after PCI, which was defined as Thrombolysis In Myocardial Infarction (TIMI) major and minor bleeding **(Supplementary Table 1)**, bleeding with various Bleeding Academic Research Consortium (BARC) grades **(Supplementary Table 2)**, or bleeding requiring blood transfusion. Major secondary endpoints included the composite endpoint of all-cause mortality, myocardial infarction, stroke, or systemic embolisation, as well as the net clinical benefit (all-cause mortality, myocardial infarction, stroke, systemic embolisation, or bleeding with BARC type 3 or higher). Other secondary endpoints included the individual components of the composite endpoints, as described in detail elsewhere[10]. Clinical follow-up was performed at 1, 3, 6, and 12 months after randomisation in a similar manner as an outpatient visit; if this was not possible, then a telephone interview or survey with a letter was permitted. Because this study had an open-label design, the clinical endpoints were assessed and classified by the Endpoint Assessment Committee whose members were blinded to the assigned treatment at the time of the outcome evaluation.

STATISTICAL ANALYSIS

This study was designed to evaluate and compare the safety of one-month and six-month $P2Y_{12}$ inhibitor treatment in combination with aspirin and apixaban in AF patients who require drug-eluting stent implantation. Our hypothesis was that the incidence of bleeding events in this population would be lower with shorter (one-month) $P2Y_{12}$ inhibitor treatment.

In the APPRAISE-2 trial which evaluated the efficacy of apixaban when added to DAPT in patients with acute coronary syndrome, the incidence of any bleeding events was 18.5% in the apixaban group and 8.4% in the placebo group[11]. Assuming an incidence of the primary endpoint of 15% for six-month $P2Y_{12}$ inhibitor treatment, a sample size of 550 patients was calculated to be necessary to detect a risk reduction of 50% associated with withdrawing the $P2Y_{12}$ inhibitor from triple therapy at one month, with 80% power and an α level of 0.05. Accounting for loss to follow-up, the target sample size for this study was established as 600 patients (300 patients per group). However, because of slow enrolment, further enrolment was stopped after 210 patients had been enrolled. The study was continued until all enrolled patients had been followed up for a minimum of six months.

Continuous variables are presented as means with standard deviations or medians and interquartile ranges, as appropriate. The unpaired t-test or Wilcoxon rank-sum test was used to compare the two groups. Categorical variables are reported as absolute values and percentages and were compared using Fisher's exact test.

Clinical outcomes were analysed based on an intention-to-treat principle. No multiplicity adjustment was made for the comparison of primary and secondary endpoints. The primary endpoint was estimated using the Kaplan-Meier method, and differences between groups were evaluated using the log-rank test. The hazard ratio (HR) and its 95% confidence interval (CI) for group comparisons were estimated using a Cox proportional hazards model that included the treatment regimen as a covariate stratified according to age, presence of acute coronary syndrome, and HAS-BLED score. Pre-specified subgroup analyses of the primary endpoint were performed.

In all analyses, $p<0.05$ was considered significant. All statistical analyses were performed by biostatisticians (M. Gosho and T. Ohigashi) using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

STUDY POPULATION

Between December 2015 and March 2018, a total of 210 eligible patients from 66 participating centres in Japan were enrolled. After excluding two patients who withdrew consent, our analysis included 208 patients who completed the trial (one-month group, 102 patients; six-month group, 106 patients) **(Figure 1)**. Although the study had originally aimed to enrol 600 patients (300 per group), enrolment was terminated after a sample size of 210 patients was reached because of slow enrolment.

The baseline patient characteristics **(Table 1)** were well balanced between the two groups, except for the prevalence of prior myocardial infarction. There were no significant differences between groups regarding lesion characteristics or procedural details **(Table 2)**. The prescribed antithrombotic drugs at enrolment and at 1, 3, 6, and 12 months after randomisation are shown in **Supplementary Figure 1**. The study was continued until all enrolled patients had been followed up for a minimum of six months. The rates of completing 12 months of follow-up were 33% for the one-month group and 31% for the six-month group (p=0.77). The median and interquartile ranges of the follow-up

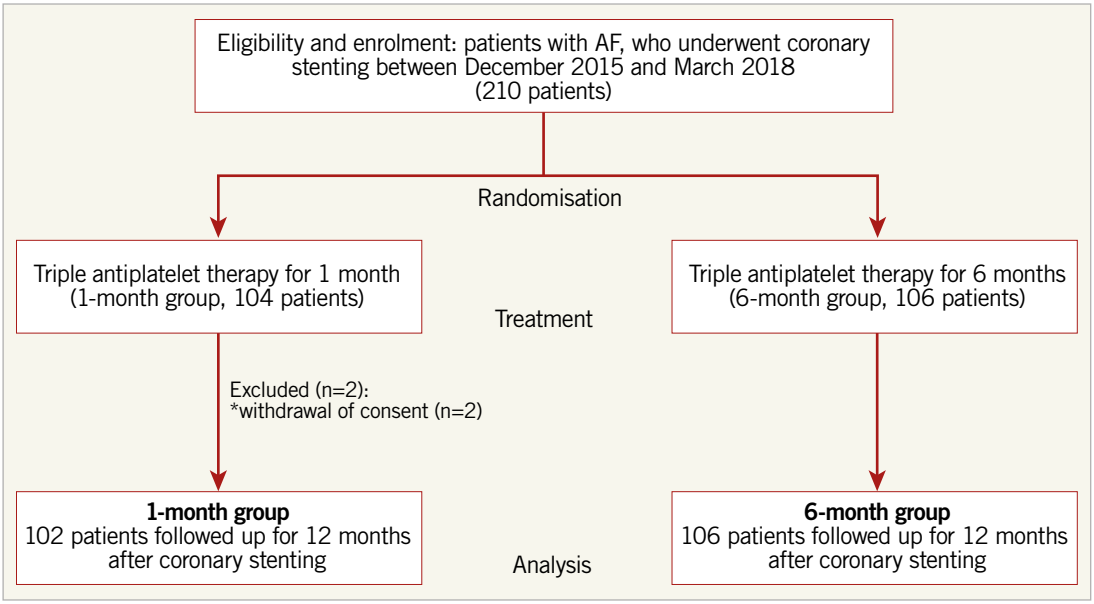

Figure 1. *Study flow chart. AF: atrial fibrillation*

Table 1. Baseline characteristics.

Characteristic		Duration of $P2Y_{12}$ inhibitor		*p*-value
		1 month (n=102)	6 months (n=106)	
Age, years		73.2±6.9	72.1±9.4	0.34
Age ≥75 years		48 (47%)	44 (42%)	0.49
Male		80 (78%)	85 (80%)	0.86
Body mass index, kg/m^2		24.6±3.5	24.5±3.2	0.80
Hypertension		75 (75%)	69 (65%)	0.13
Diabetes mellitus		47 (46%)	48 (45%)	1.00
Insulin use		4 (4%)	5 (5%)	1.00
Dyslipidaemia		77 (77%)	85 (80%)	0.61
Current smoker		12 (12%)	20 (19%)	0.18
Chronic kidney disease		10 (10%)	17 (16%)	0.22
Acute coronary syndrome		17 (17%)	18 (17%)	1.00
Left ventricular ejection fraction, %		60.4±11.9	60.2±11.8	0.90
Prior myocardial infarction		9 (9%)	20 (19%)	0.047
Prior heart failure		26 (26%)	28 (26%)	1.00
Prior stroke		18 (18%)	12 (11%)	0.24
Prior gastrointestinal bleeding		3 (3%)	3 (3%)	1.00
Malignancy		11 (11%)	7 (7%)	0.33
Type of atrial fibrillation	Paroxysmal	44 (44%)	54 (51%)	0.70
	Persistent	23 (23%)	19 (18%)	
	Long persistent	14 (14%)	16 (15%)	
	Permanent	19 (19%)	17 (16%)	
$CHADS_2$ score		2.4±1.3	2.1±1.2	0.18
CHA_2DS_2-VASc score		3.9±1.6	3.6±1.5	0.31
HAS-BLED score		2.3±0.8	2.3±0.8	0.82
Number of diseased vessels	One vessel	66 (66%)	76 (72%)	0.76
	Two vessels	25 (25%)	23 (22%)	
	Three vessels	8 (8%)	5 (5%)	
	Bypass graft	1 (1%)	1 (1%)	
Medications at enrolment				
Aspirin		99 (99%)	103 (98%)	1.00
Apixaban	10 mg/day	64 (73%)	66 (73%)	1.00
	5 mg/day	24 (27%)	24 (27%)	
$P2Y_{12}$ inhibitor	Clopidogrel	55 (56%)	63 (61%)	0.48
	Prasugrel	44 (44%)	40 (39%)	
Antiulcer drug	Histamine type 2 receptor blocker	6 (7%)	9 (10%)	0.51
	Proton pump inhibitor	81 (93%)	78 (89%)	
Statin		74 (74%)	84 (80%)	0.32
Beta-blocker		53 (53%)	59 (56%)	0.68
ACE inhibitor		19 (19%)	16 (15%)	0.58
ARB		32 (32%)	40 (38%)	0.38
Calcium blocker		50 (50%)	41 (39%)	0.12
NSAID		6 (6%)	7 (7%)	1.00

Values represent mean±standard deviation or frequency (percentage). ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; NSAID: non-steroidal anti-inflammatory drug

Table 2. Lesion characteristics and procedure details.

Characteristic		Duration of $P2Y_{12}$ inhibitor		*p*-value
		1 month (n=102)	6 months (n=106)	
Target vessel	Left anterior descending artery	48 (48%)	59 (56%)	0.74
	Left circumflex artery	21 (21%)	19 (18%)	
	Right coronary artery	30 (30%)	26 (25%)	
	Bypass graft	1 (1%)	1 (1%)	
Type of lesion	Type A	29 (29%)	17 (16%)	0.18
	Type B1	23 (23%)	29 (28%)	
	Type B2	26 (26%)	30 (29%)	
	Type C	22 (22%)	29 (28%)	
Chronic total occlusion		3 (3%)	7 (7%)	0.33
Bifurcation lesion		14 (14%)	24 (23%)	0.11
PCI procedure				
Stent diameter, mm		2.9±0.5	3.0±0.5	0.86
Stent length, mm		23.4±8.7	25.0±9.3	0.21
Number of stents implanted	1	89 (89%)	83 (80%)	0.084
	≥2	11 (11%)	21 (20%)	
Maximum pressure, atm		15.6±4.5	16.0±4.9	0.63
Contrast volume, mL		129.1±56.0	133.4±58.5	0.59
Use of IVUS		93 (93%)	99 (94%)	0.78
Use of IABP		1 (1%)	0	0.49

Values represent mean±standard deviation or frequency (percentage). IABP: intra-aortic balloon pump; IVUS: intravascular ultrasound; PCI: percutaneous coronary intervention

period were 11.7 months (6.0, 12.2) and 10.0 months (5.7, 12.1), for the one-month group and six-month group, respectively (p=0.37).

CLINICAL OUTCOMES

Within 12 months after PCI, the primary endpoint (any bleeding) occurred in 11.8% of patients in the one-month group and in 16.0% of patients in the six-month group (HR 0.70, 95% CI: 0.33-1.47; p=0.35) **(Table 3, Figure 2A)**. The major secondary composite endpoint occurred in 9.8% of patients in the one-month group and 2.8% of patients in the six-month group (HR 3.00, 95% CI: 0.82-10.94; p=0.096), with the difference explained mainly in terms of the higher incidence of non-cardiac death for the one-month group **(Table 3, Figure 2B)**. There was no significant difference in the net clinical benefit of the one-month and six-month groups (10.8% vs 5.7%; HR 1.70, 95% CI: 0.63-4.61; p=0.30) **(Table 3, Figure 2C)**.

Regarding the individual secondary endpoints, non-cardiac death was observed more frequently in the one-month group than in the six-month group (3.9% vs 0%; p=0.048); there were three cancer-related deaths and one pneumonia-related death. Stent thrombosis and myocardial infarction occurred in only one patient (in the one-month group) **(Table 3)**.

Finally, the pre-specified subgroup analysis revealed no significant interactions with the lack of treatment effect, which was consistent across all pre-specified subgroups **(Figure 3)**.

Table 3. Clinical outcomes.

Outcome		Duration of $P2Y_{12}$ inhibitor				Hazard ratio (95% CI)	*p*-value
		1 month (n=102)		6 months (n=106)			
		No. of events (%)	Event rate per 100 patient-years	No. of events (%)	Event rate per 100 patient-years		
Primary endpoint							
Any bleeding		12 (11.8%)	15.7	17 (16.0%)	24.0	0.70 (0.33, 1.47)	0.35
TIMI major bleeding		2 (2.0%)	2.5	4 (3.8%)	5.2	0.52 (0.09, 2.84)	0.45
TIMI minor bleeding		6 (5.9%)	15.5	3 (2.8%)	7.9	1.97 (0.49, 7.90)	0.34
According to the BARC criteria	type 1 bleeding	3 (3%)		10 (9%)			
	type 2 bleeding	4 (4%)		3 (3%)			
	type 3a bleeding	3 (3%)		1 (1%)			
	type 3b bleeding	0		1 (1%)			
	type 3c bleeding	1 (1%)		1 (1%)			
	type 4 bleeding	0		0			
	type 5a bleeding	0		0			
	type 5b bleeding	1 (1%)		1 (1%)			
Bleeding requiring blood transfusion		1 (1%)		0			
Secondary endpoints							
Composite outcome: all-cause death, myocardial infarction, stroke, or systemic embolisation		10 (9.8%)	12.8	3 (2.8%)	3.9	3.00 (0.82, 10.94)	0.096
Net clinical benefit: all-cause death, myocardial infarction, stroke, or systemic embolisation and bleeding complication (BARC type 3 or higher)		11 (10.8%)	14.3	6 (5.7%)	7.9	1.70 (0.63, 4.61)	0.30
All-cause death		6 (5.9%)	7.7	2 (1.9%)	2.6	2.83 (0.57, 14.06)	0.20
Cardiovascular death		2 (2.0%)	2.5	2 (1.9%)	2.6	0.97 (0.13, 6.93)	0.97
Non-cardiac death		4 (3.9%)	5.2	0	0	–	–
Myocardial infarction		1 (1.0%)	1.3	0	0	–	–
Hospitalisation due to unstable angina		0	0	1 (0.9%)	1.3	–	–
Stroke		3 (2.9%)	3.8	2 (1.9%)	2.6	1.19 (0.19, 7.42)	0.85
Systemic embolisation		0	0	0	0	–	–
Stent thrombosis		1 (1.0%)	1.3	0	0	–	–
PCI		4 (3.9%)	5.0	4 (3.8%)	5.2	0.97 (0.24, 3.87)	0.96
CABG		0	0	0	0	–	–
Non-cardiac surgery		8 (7.8%)	10.3	6 (5.7%)	8.0	1.31 (0.45, 3.78)	0.62
Emergent hospitalisation due to heart failure		2 (2.0%)	2.6	3 (2.8%)	3.9	0.64 (0.11, 3.82)	0.62
Unscheduled dose reduction or discontinuation of study drugs		10 (9.8%)	12.8	20 (18.9%)	26.0	0.51 (0.24, 1.08)	0.079

BARC: Bleeding Academic Research Consortium; CABG: coronary artery bypass grafting; CI: confidence interval; PCI: percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction

Discussion

The SAFE-A study was the first randomised trial comparing one month and six months of $P2Y_{12}$ inhibitor therapy, combined with aspirin and apixaban, for patients with AF who require coronary stenting. The major findings were that one-month $P2Y_{12}$ inhibitor therapy was not superior to six-month $P2Y_{12}$ inhibitor therapy as part of a triple antithrombotic therapy regimen to decrease the risk of bleeding events. Furthermore, no significant differences were found in the rates of ischaemic coronary events between one-month and six-month $P2Y_{12}$ inhibitor therapy when combined with apixaban-based dual therapy.

In the present study, the incidence of the primary endpoint tended to be lower in the one-month group than in the six-month group (11.8% vs 16.0%; HR 0.70, 95% CI: 0.33-1.47; p=0.35).

The SAFE-A study failed to demonstrate the superiority of short-term (one-month) $P2Y_{12}$ inhibitor therapy for reducing bleeding complications. The lack of statistical significance was probably due to the limited number of patients enrolled. Although the study had originally aimed to enrol 600 patients (300 per group), enrolment was terminated after a sample size of 210 patients was reached. Slow enrolment was probably related to the physicians' concerns regarding the increased risk of bleeding associated with prolonged triple therapy.

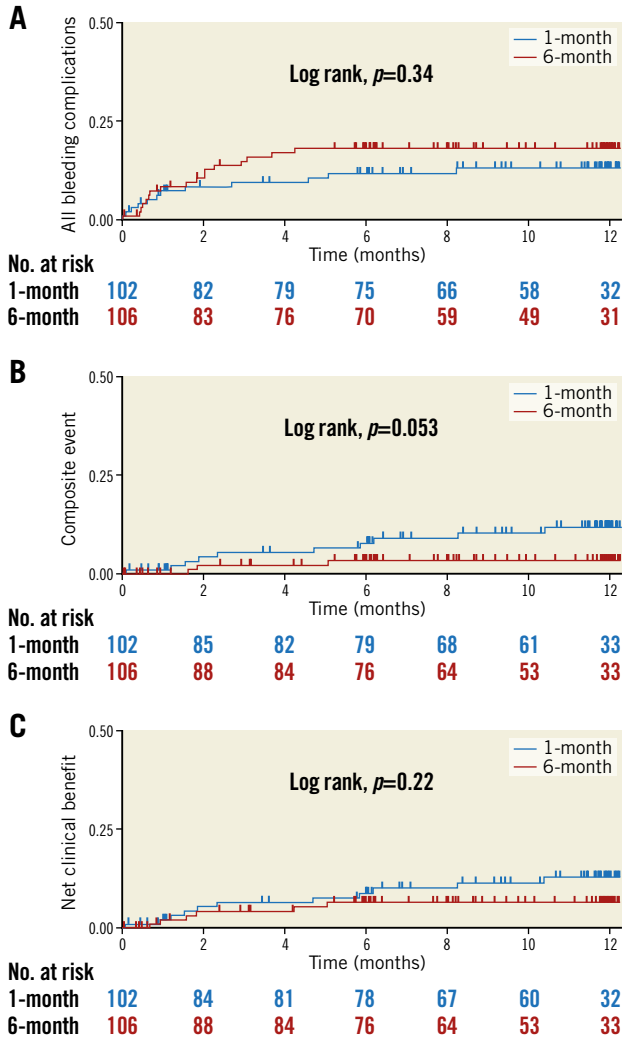

Figure 2. *Kaplan-Meier curves. Cumulative incidence of the primary endpoint (any bleeding events; A), composite secondary endpoint (all-cause mortality, myocardial infarction, stroke, or systemic embolisation; B), and net clinical benefit (all-cause mortality, myocardial infarction, stroke, systemic embolisation, or BARC type 3 or higher bleeding; C) within 12 months after coronary stenting. BARC: Bleeding Academic Research Consortium*

The balance between the ischaemic risk and bleeding risk is particularly important for patients who require anticoagulation or antiplatelet treatment. Regarding patients without AF, shorter (three- to six-month) DAPT was associated with a significant reduction in major bleeding events, without increasing the risk of ischaemic events, compared with the standard 12 months of DAPT[12]. However, current evidence regarding the safety and effectiveness of triple therapy (combination of dual antiplatelet and anticoagulant treatments) for patients with AF remains limited. Recently, several randomised controlled trials combining NOAC and antiplatelet therapy have aimed to address such limitations and to compare rivaroxaban-, dabigatran-, and apixaban-based triple therapy strategies against warfarin-based triple therapy[6-8]. Recently, the AUGUSTUS trial found that the combination of apixaban and a $P2Y_{12}$ inhibitor was associated with fewer bleeding events than a warfarin-based strategy (10.5% vs 14.7%; HR 0.69, 95% CI: 0.58-0.81) among patients with AF who presented with recent acute coronary syndrome, or who required PCI[8]. In both arms, the addition of aspirin compared to placebo was associated with an increased incidence of bleeding (16.1% vs 9.0%; HR 1.89, 95% CI: 1.59-2.24). The results of recent trials suggested that NOAC-based strategies should be preferred over warfarin-based strategies to reduce the risk of bleeding in patients with AF who require coronary stenting.

The SAFE-A study exhibited two main differences from previous studies. First, early withdrawal of the $P2Y_{12}$ inhibitor from NOAC-based strategies represents a unique feature of this study design. Previous studies examined the safety and efficacy of the combination of NOAC and a $P2Y_{12}$ inhibitor, and withdrawing aspirin, as compared to warfarin-based strategies. Second, in this study, approximately 40% of patients received prasugrel as the $P2Y_{12}$ inhibitor, whereas most patients received clopidogrel as the $P2Y_{12}$ inhibitor in previous studies. It is unclear whether clopidogrel or aspirin should be stopped early to reduce the risk of bleeding for patients receiving NOAC-based antithrombotic therapy. Withdrawing aspirin from DAPT after stent implantation raises concerns about the loss of protection against coronary ischaemic events. The effect and safety of very early withdrawal of aspirin therapy (at one to two weeks) remain topics of debate because the first weeks after PCI are known to represent the period with the highest risk for coronary ischaemic events. The AUGUSTUS trials did find a slightly smaller number of coronary ischaemic events among patients who used aspirin compared to those who did not (2.9% vs 3.6%; HR 0.81, 95% CI: 0.59-1.12), although event rates were low and the trial was not adequately powered to assess differences in individual ischaemic outcomes[8]. Recent meta-analysis showed a significant increase of stent thrombosis (risk ratio 1.59, 95% CI: 1.01-2.50; p=0.04) with a double therapy of NOAC and $P2Y_{12}$ inhibitor without aspirin, as compared to triple therapy[13]. Another matter of concern is the polymorphism of cytochrome P450 2C19 (CYP2C19), which affects the pharmacokinetics of clopidogrel[14]. Poor CYP2C19 metabolism, which is associated with a lack of response to clopidogrel, is noted among approximately 20% of the Asian population[15]. Our present results suggest that it may be feasible to withdraw the $P2Y_{12}$ inhibitor and continue aspirin and apixaban for patients with AF who require drug-eluting stent implantation. Nevertheless, the optimal antithrombotic treatment regimen for these patients remains to be clarified in further clinical studies with adequate power.

Limitations

This study had several limitations. First, the number of enrolled patients was smaller than the target sample size established based on the original design because enrolment was slow and had to be terminated prematurely. Second, due to the open-label design, we could not exclude selection bias. However, the assessment

Subgroup	N of events / total N (%) 1-month	6-month	HR	95% CI lower	upper	*p* for interaction
Age						
<75 years	4/54 (7.4)	12/62 (19.4)	0.38	0.12	1.19	0.12
≥75 years	8/48 (16.7)	5/44 (11.4)	1.33	0.44	4.07	
Gender						
Male	10/80 (12.5)	15/85 (17.6)	0.67	0.30	1.50	0.77
Female	2/22 (9.1)	2/21 (9.5)	0.92	0.13	6.54	
Diabetes						
No	6/55 (10.9)	10/58 (17.2)	0.60	0.22	1.65	0.64
Yes	6/47 (12.8)	7/48 (14.6)	0.85	0.29	2.53	
CKD						
No	10/90 (11.1)	15/89 (16.9)	0.62	0.28	1.38	0.38
Yes	2/10 (20.0)	2/17 (11.8)	1.48	0.21	10.53	
$CHADS_2$ score						
<2	1/28 (3.6)	8/35 (22.9)	0.16	0.02	1.24	0.084
≥2	11/74 (14.9)	9/71 (12.7)	1.10	0.46	2.66	
HAS-BLED						
<3	6/60 (10.0)	13/65 (20.0)	0.49	0.19	1.30	0.23
≥3	6/42 (14.3)	4/41 (9.8)	1.30	0.37	4.62	
Number of vessels						
one vessel	10/66 (15.2)	12/76 (15.8)	0.89	0.39	2.07	0.29
multivessel	2/33 (6.1)	5/28 (17.9)	0.33	0.06	1.72	
Bifurcation						
No	11/86 (12.8)	11/81 (13.6)	0.91	0.40	2.10	0.25
Yes	1/14 (7.1)	6/24 (25.0)	0.25	0.03	2.06	
Stent length						
<20 mm	3/41 (7.3)	4/40 (10.0)	0.70	0.16	3.14	0.99
≥20 mm	9/59 (15.3)	13/64 (20.3)	0.71	0.30	1.65	
Stent diameter						
<3.0 mm	5/46 (10.9)	6/42 (14.3)	0.73	0.22	2.38	0.94
≥3.0 mm	7/54 (13.0)	11/62 (17.7)	0.68	0.26	1.76	
Number of stents						
1	10/89 (11.2)	15/83 (18.1)	0.58	0.26	1.29	0.26
≥2	2/11 (18.2)	2/21 (9.5)	1.92	0.27	13.64	
$P2Y_{12}$ inhibitor						
Clopidogrel	6/55 (10.9)	10/63 (15.9)	0.60	0.22	1.65	0.55
Prasugrel	6/44 (13.6)	6/40 (15.0)	0.96	0.31	2.99	
Dose of apixaban						
5 mg/day	3/24 (12.5)	2/24 (8.3)	1.05	0.18	6.29	0.64
10 mg/day	8/64 (12.5)	13/66 (19.7)	0.65	0.27	1.57	

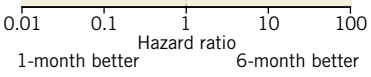

Figure 3. *Pre-specified subgroup analysis of the primary endpoint. Patients were stratified according to the duration of triple antithrombotic therapy (one-month group vs six-month group). Data are presented as the number of patients with events, crude incidence rates, and hazard ratio (HR) with 95% confidence interval (CI). Data for the six-month group were used as a reference. CKD: chronic kidney disease*

of endpoints was blinded. Third, approximately 40% of patients included in this study were using prasugrel. The approved dose of prasugrel in Japan (20 mg and 3.75 mg/day for loading and maintenance, respectively) is lower than that approved in Western countries. Because the present study involved Japanese patients, the findings cannot be generalised to other ethnic populations. Fourth, unscheduled dose reduction or discontinuation of study drugs was performed for 9.8% and 18.9% of patients in the one-month group and six-month group, respectively, which might have affected the results of the study.

Conclusions

SAFE-A is the first randomised trial to compare one-month and six-month $P2Y_{12}$ inhibitor therapy in combination with aspirin and apixaban for patients with AF who underwent PCI with drug-eluting stent implantation. The study was prematurely terminated because of slow enrolment and was not powered to assess the differences in the primary endpoint. We could not confirm that early stopping of the $P2Y_{12}$ inhibitor can reduce bleeding events after PCI for patients with AF.

Impact on daily practice

SAFE-A is the first randomised trial to compare one-month and six-month therapy with a $P2Y_{12}$ inhibitor combined with aspirin and apixaban to prevent major adverse cardiovascular events for AF patients who require coronary stenting. The unique approach involved withdrawing the $P2Y_{12}$ inhibitor at one month after stenting. However, the results failed to show the superiority of such short-term $P2Y_{12}$ inhibitor treatment for reducing bleeding events, probably because of the inadequate statistical power.

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Conflict of interest statement

K. Aonuma has received research grants from Bristol-Myers Squibb K.K., and belongs to departments endowed by commercial entities Boston Scientific Corporation, Japan Lifeline Co., Ltd., Nihon Kohden Corporation, BIOTRONIK Japan, Inc., Toray Industries, Inc., Boehringer Ingelheim GmbH, and Century Medical, Inc. During the study, M. Gosho received lecture and/or consultant fees from Daiichi Sankyo, Ferring Pharmaceuticals, Novartis, and Asahikasei Pharma. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Study organisation.

Supplementary Figure 1. The prescription of antithrombotic drugs at enrolment and at 1, 3, 6, and 12 months after randomisation ($P2Y_{12}$ inhibitor, A; apixaban, B; and aspirin, C) for the one-month group and six-month group. Data are presented as a percentage of each drug.

Supplementary Table 1. Definition of the Thrombolysis In Myocardial Infarction (TIMI) bleeding criteria.

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The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00920

Supplementary data

Supplementary Appendix 1. Study organisation

Principal investigator

Kazutaka Aonuma, Cardiovascular Division, Faculty of Medicine, University of Tsukuba

Steering committee

Akihiko Nogami, Akira Sato, and Tomoya Hoshi, Cardiovascular Division, Faculty of Medicine, University of Tsukuba

Safety and data monitoring committee

Yoshifusa Aizawa, Tachikawa General Hospital/ Department of Cardiovascular Medicine, Niigata University
Yasuki Kihara, Department of Cardiovascular Medicine, Hiroshima University
Masato Nakamura, Department of Cardiovascular Medicine, Toho University Ohashi Medical Center
Yoshihiro Morino, Department of Cardiology, Department of Internal Medicine, Iwate Medical University

Clinical event assessment committee

Yoshio Kobayashi, Department of Cardiovascular Medicine, Chiba University
Hiroshi Tada, Department of Cardiovascular Medicine, University of Fukui
Akira Tamaoka, Department of Neurology, Faculty of Medicine, University of Tsukuba

Study coordinating centre, data centre, and quality control

Hiroyuki Hosokawa, Masahiro Sakai, Eriko Onose, and Koichi Hashimoto, Tsukuba Clinical Research & Development Organization (T-CReDO), University of Tsukuba

Statistical analysis

Masahiko Gosho and Tomohiro Ohigashi, Department of Biostatistics, Faculty of Medicine, University of Tsukuba

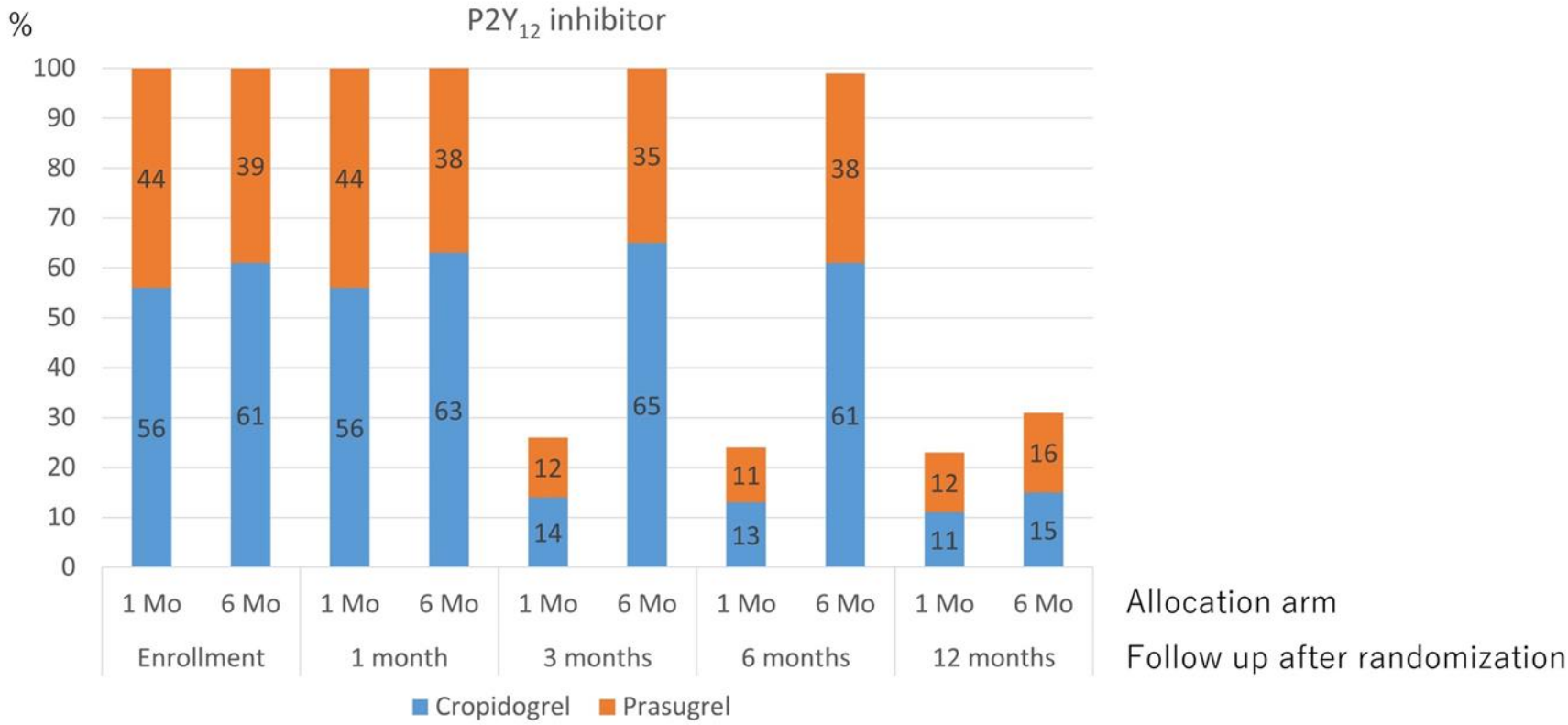
Study investigators

1. University of Tsukuba	Kazutaka Aonuma
2. Ayase Heart Hospital	Naoki Nozaki
3. Ibaraki Prefectural Central Hospital	Noriyuki Takeyasu
4. Ibaraki Seinan Medical Center Hospital	Hiroshi Maeda
5. Iwaki Kyoritsu Hospital	Masafumi Sugi

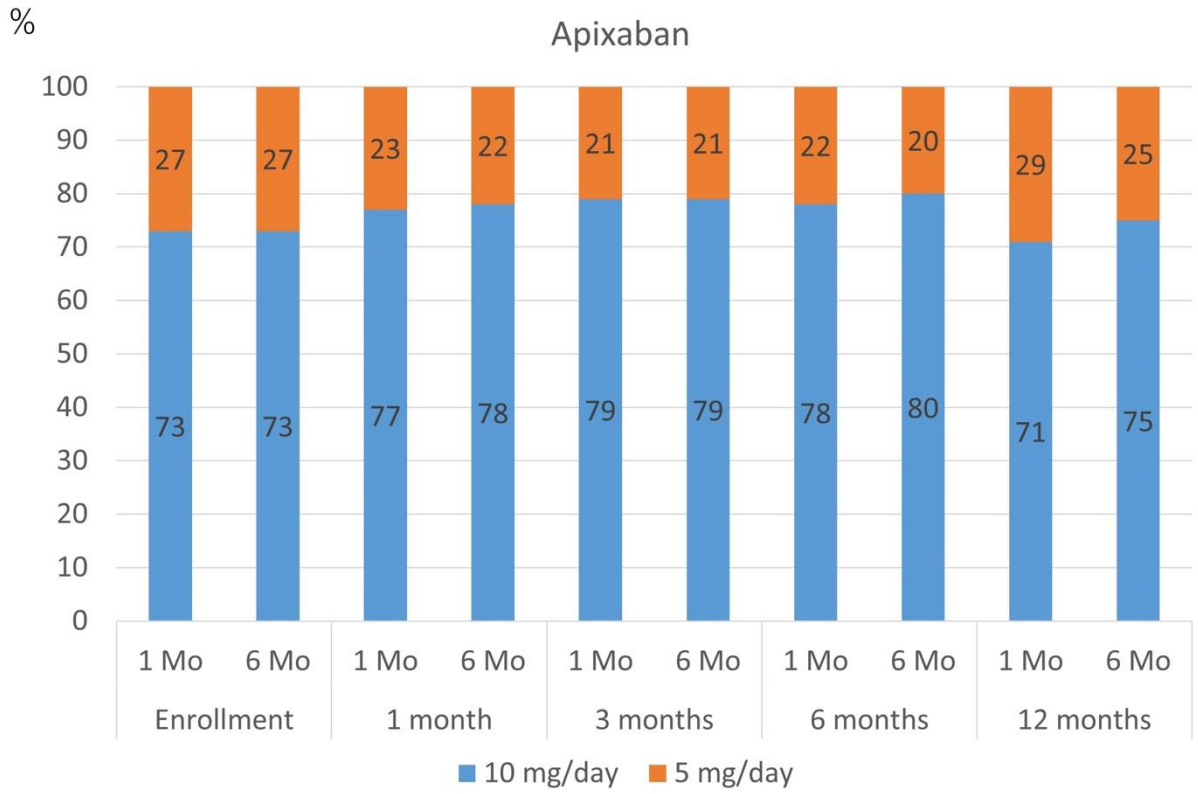
6. Iwate Medical University	Tetsuya Fusazaki
7. Iwate Prefectural Central Hospital	Akihiro Nakamura
8. Ome Municipal General Hospital	Kenichiro Otomo
9. Ogaki Municipal Hospital	Itsuro Morishima
10. Osaka City University Graduate School of Medicine	Minoru Yoshiyama
11. Ohta Nishinouchi Hospital	Hirohito Takeda
12. Kagoshima Medical Center	Norihito Nuruki
13. Kamagaya General Hospital	Takeo Nishimori
14. Gunma Prefectural Cardiovascular Center	Hiroshi Hoshizaki
15. National Hospital Organization Disaster Medical Center	Yasuhiro Sato
16. Saitama Red Cross Hospital	Yutaka Matsumura
17. Sakurabashi Watanabe Hospital	Kenji Fujii
18. Sapporo Heart Center, Sapporo Cardiovascular Clinic	Daitaro Kanno
19. Shuwa General Hospital	Susumu Adachi
20. New Tokyo Hospital	Sunao Nakamura
21. Soka Municipal Hospital	Hiroyuki Okada
22. Moriya Daiichi General Hospital	Masae Endo
23. Takase Clinic	Hiroshi Fukazawa
24. Chikamori Hospital	Masahiko Fukatani
25. Chiba University	Hideki Kitahara
26. Tsukuba Medical Center Hospital	Yuichi Noguchi
27. Tsuchiura Kyodo General Hospital	Tsunekazu Kakuta
28. Tokai University Hachioji Hospital	Yoshinori Kobayashi
29. Tokyo Medical University Ibaraki Medical Center	Norihiro Abe
30. Tokyo Metropolitan Hiroo Hospital	Seiji Fukamizu
31. Tokyo Metropolitan Bokutoh Hospital	Daisuke Abe
32. Tokushima Red Cross Hospital	Koichi Kishi
33. Toda Chuo General Hospital	Takashi Uchiyama
34. Dokkyo Medical University Koshigaya Hospital	Isao Taguchi
35. Nagano Red Cross Hospital	Tatsuya Usui
36. Nagoya Daini Red Cross Hospital	Mamoru Nanasato
37. Hitachi General Hospital	Yutaka Eki
38. Hitachinaka General Hospital	Takayoshi Yamanouchi
39. Hiratsuka Kyosai Hospital	Yuko Onishi
40. Hiroshima City Hospital	Fumiharu Miura
41. Hiroshima University Hospital	Yukiko Nakano
42. University of Fukui Hospital	Hiroyasu Uzui
43. Fukushima Medical University	Yasuchika Takeishi

44. Mito Medical Center	Tomomi Koizumi
45. Mito Kyodo General Hospital	Shigeyuki Watanabe
46. Mito Saiseikai General Hospital	Ohhira Kouji
47. Mito Brain Heart Center	Yoshiki Uehara
48. Miyazaki Medical Association Hospital	Yoshisato Shibata
49. Musashino Red Cross Hospital	Toshihiro Nozato
50. Yamagata Prefectural Central Hospital	Akio Fukui
51. Yamagata University Hospital	Takanori Arimoto
52. Yamaguchi University Hospital	Masafumi Yano
53. Yamanashi Prefectural Central Hospital	Ken Umetani
54. Yamanashi Kousei Hospital	Kuniyoshi Matsumura
55. Yokosuka Kyosai Hospital	Hiroyuki Hikita
56. Yokohama Sakae Kyosai Hospital	Ichiro Michishita
57. Yokohama Rosai Hospital	Kazuhito Yumoto
58. Kurume University	Takafumi Ueno
59. Sakakibara Memorial Hospital	Tetsuya Tobaru
60. Kanoya Heart Center	Hidekazu Arai
61. Jichi Medical University School of Medicine	Kazuomi Kario
62. Asahikawa Medical University	Naoyuki Hasebe
63. Yokohama Shintoshi Neurosurgical Hospital	Taichiro Hayase
64. Sendai Kousei Hospital	Takashi Matsumoto
65. Oita University	Naohiko Takahashi
66. Mashiko Hospital	Shogo Shimizu

Supplemental Figure 1 A



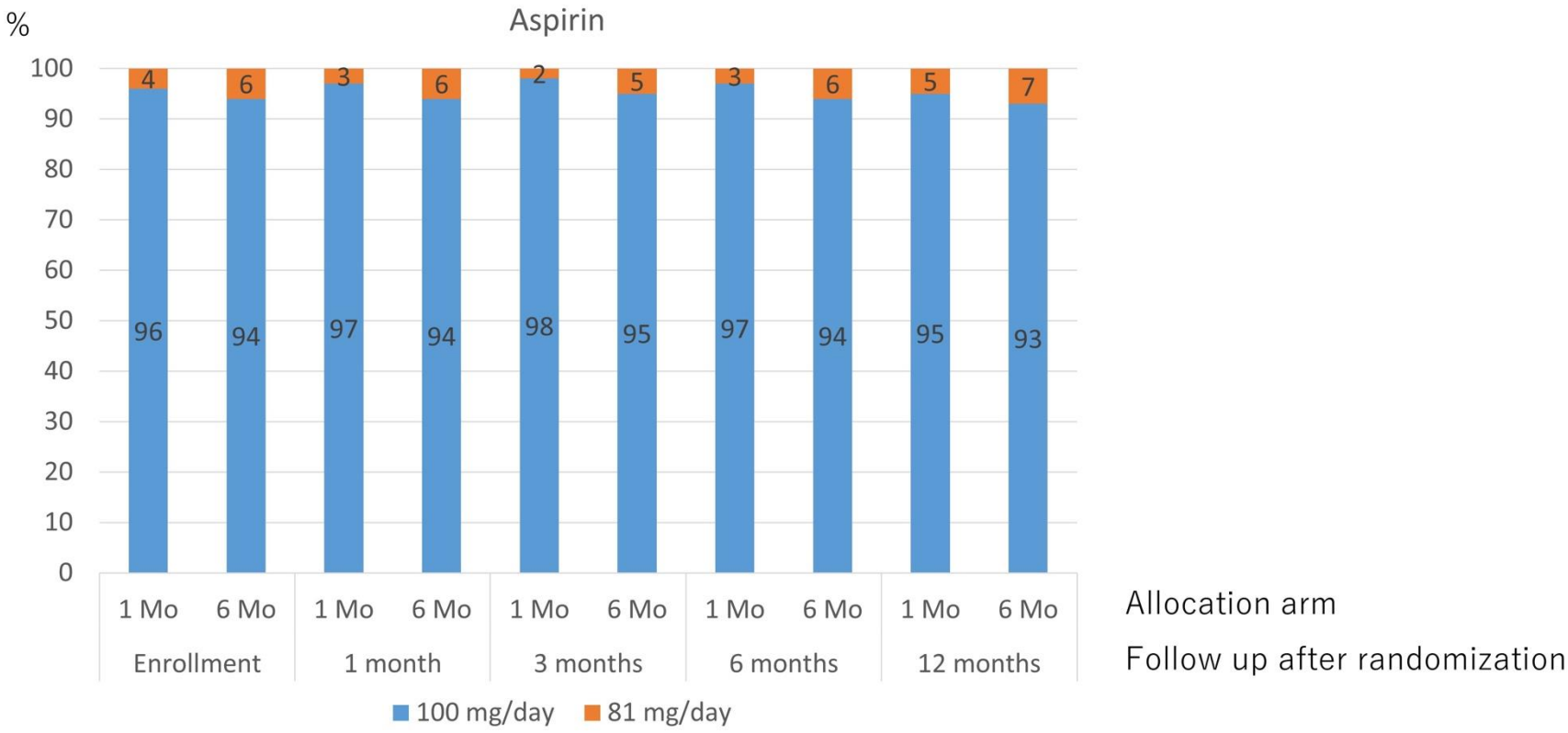
Supplemental Figure 1 B



Allocation arm

Follow up after randomization

Supplemental Figure 1 C



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Supplementary Table 1. Definition of the Thrombolysis In Myocardial Infarction (TIMI) bleeding criteria.

Major bleeding

- Any symptomatic intracranial haemorrhage
- Clinically overt signs of haemorrhage (including imaging) associated with a drop in haemoglobin of ≥5 g/dL or a ≥15% absolute decrease in haematocrit)
- Fatal bleeding (bleeding that directly results in death within seven days)

Minor bleeding

- Clinically overt sign of haemorrhage (including imaging) resulting in haemoglobin drop of 3 to <5 g/dL or ≥10% decrease in haematocrit
- No observed blood loss: ≥4 g/dL decrease in the haemoglobin concentration or ≥12% decrease in haematocrit

Minimal bleeding

- Any overt bleeding event that does not meet the criteria above
- Any clinically overt sign of haemorrhage (including imaging) associated with a <3 g/dL decrease in haemoglobin concentration or <9% decrease in haematocrit

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Supplementary Table 2. Bleeding Academic Research Consortium (BARC) definition for bleeding.

Type 0: No bleeding

Type 1: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalisation, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2: Any overt, actionable sign of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring non-surgical, medical intervention by a healthcare professional, (2) leading to hospitalisation or increased level of care, or (3) prompting evaluation

Type 3:

Type 3a

Overt bleeding plus haemoglobin drop of 3 to <5 g/dL* (provided haemoglobin drop is related to bleed)

Any transfusion with overt bleeding

Type 3b

Overt bleeding plus haemoglobin drop ≥5 g/dL* (provided haemoglobin drop is related to bleed)

Cardiac tamponade

Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid)

Bleeding requiring intravenous vasoactive agents

Type 3c

Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation, does include intraspinal)

Subcategories confirmed by autopsy or imaging or lumbar puncture

Intraocular bleed compromising vision

Type 4: CABG-related bleeding

Perioperative intracranial bleeding within 48 hrs

Reoperation after closure of sternotomy for the purpose of controlling bleeding

Transfusion of ≥5 U whole blood or packed red blood cells within a 48-hr period†

Chest tube output 2L within a 24-hr period

Type 5: Fatal bleeding

Type 5a

Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b

Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

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Platelet transfusion should not be included in these definitions.

*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1 g/dL haemoglobin).

†Cell saver products are not counted.

CABG: coronary artery bypass graft