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Title: **Short-Duration Triple Antithrombotic Therapy for Atrial Fibrillation Patients Who Require Coronary Stenting: Results of the SAFE-A Study.**

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DOI: 10.4244/EIJ-D-19-00920

Citation: Hoshi T, Sato A, Hiraya D, Watabe H, Takeyasu N, Nogami A, Ohigashi T, Gosho M, Ieda M, Aonuma K, for the SAFE-A Investigators. Short-Duration Triple Antithrombotic Therapy for Atrial Fibrillation Patients Who Require Coronary Stenting: Results of the SAFE-A Study. *EuroIntervention* 2020; Jaa-739 2020, doi: 10.4244/EIJ-D-19-00920

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Manuscript submission date: 05 October 2019

Revisions received: 17 January 2020, 10 February 2020

Accepted date: 20 February 2020

Online publication date: 25 February 2020

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Short-Duration Triple Antithrombotic Therapy for Atrial Fibrillation Patients Who Require Coronary Stenting: Results of the SAFE-A Study

Short title: SAFE-A study

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The list of the SAFE-A investigators can be found in Supplemental Appendix.

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Conflict of Interest Disclosures

K. Aonuma has received research grants from Bristol-Myers Squibb KK, and belongs to departments endowed by commercial entities Boston Scientific Corporation, Japan Lifeline Co., Ltd., Nihon Cohden 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. All other authors have reported nothing to disclose.

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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 randomized controlled trial that compared 1-month and 6-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 Thrombosis in Myocardial Infarction with major/minor bleeding, bleeding with various Bleeding Academic Research Consortium

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grades, or bleeding requiring blood transfusion within 12 months after stenting. The study aimed to enroll 600 patients, but enrollment was slow. Enrollment was terminated prematurely after enrolling 210 patients (72.7±8.2 years; 81% men). The incidence of the primary endpoint did not differ between the 1-month and 6-month groups (11.8% vs 16.0%; hazard ratio, 0.70; 95% confidence interval, 0.33–1.47; $P = 0.35$).

Conclusions: The study evaluated the safety of withdrawing the $P2Y_{12}$ inhibitor from triple antithrombotic prescription 1 month after coronary stenting. However, enrollment was prematurely terminated because it was slow. Therefore, statistical power was not sufficient to assess the differences in the primary endpoint.

(Abstract word count: 200 words)

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Key words: drug-eluting stent, atrial fibrillation, anticoagulant therapy

Abbreviations

AF: atrial fibrillation

BARC: Bleeding Academic Research Consortium

CI: confidence interval

CYP2C19: cytochrome P450 2C19

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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: Thrombosis in Myocardial Infarction

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Condensed abstract

The SAFE-A is a randomized controlled trial that compared 1-month and 6-month $P2Y_{12}$ inhibitor therapy in combination with aspirin and apixaban for patients with atrial fibrillation who require coronary stenting. The primary endpoint was defined as the incidence of any bleeding (Thrombosis in Myocardial Infarction with major/minor bleeding, bleeding with various Bleeding Academic Research Consortium grades, or bleeding requiring blood transfusion). The study was prematurely terminated because of slow enrollment and did not carry sufficient statistical power to assess the differences in the primary endpoint.

(85 words)

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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 two-fold to–three-fold 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 after coronary stent implantation [5]. To date, several randomized 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 the rate of 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

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agents should be administered for 1 or 6 months, depending on the individual patient's risk for ischemia 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 (1 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 implantations.

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METHODS

Study Design

The SAFE-A study is a multicenter, prospective, randomized, open-label, clinical trial that compared 1-month and 6-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

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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]. This 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. This study was registered in the UMIN Clinical Trial Registry (UMIN000015923).

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Randomization and Treatment

Within 72 hours after PCI, eligible patients were randomized in a 1:1 ratio to receive a $P2Y_{12}$ inhibitor (clopidogrel or prasugrel) for either 1 month or 6 months, in combination with both aspirin and apixaban (triple therapy). Randomization 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)

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was used as the $P2Y_{12}$ inhibitor at the discretion of the treating physician at the time of enrollment.

Endpoints and Follow-up

Patients were evaluated at 1, 3, 6, and 12 months after randomization 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 Thrombosis in Myocardial Infarction (TIMI) with major and minor bleeding (Supplemental Table 1), bleeding with various Bleeding Academic Research Consortium (BARC) grades (Supplemental Table 2), or bleeding requiring blood transfusion. Major secondary endpoints included the composite endpoint of all-cause mortality, myocardial infarction, stroke, or systemic embolization, as well as the net clinical benefit (all-cause mortality, myocardial infarction, stroke, systemic embolization, 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 randomization in a similar manner as an outpatient visit; if this was not possible, then a

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telephone interview or survey with a letter were permitted. Because this study had an open-label design, the clinical endpoints were assessed and classified by the Endpoint Assessment Committee who 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 1-month and 6-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 (1-month) $P2Y_{12}$ inhibitor treatment.

In the APPRAISE-2 trial that 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 6-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 1 month,

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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 enrollment, further enrollment was stopped after 210 patients had been enrolled. The study was continued until all enrolled patients had been followed-up for a minimum of 6 months.

Continuous variables were 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 were reported as absolute values and percentages and were compared using Fisher's exact test.

Clinical outcomes were analyzed 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 hazard 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 primary endpoint were performed.

In all analyses, $P < 0.05$ was considered significant. All statistical analyses were

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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 centers in Japan were enrolled. After excluding two patients who withdrew consent, our analysis included 208 patients who completed the trial (1-month group, 102 patients; 6-month group, 106 patients) (Figure 1). Although the study had originally aimed to enroll 600 patients (300 per group), enrollment was terminated after a sample size of 210 patients was reached because of slow enrollment.

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 enrollment and at 1, 3, 6, and 12 months after randomization are shown in Supplemental Figure 1. The study was continued until all enrolled patients had been followed-up for a minimum of 6 months.

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The rates of completing12 months of follow-up were 33% for the 1-month group and 31% for the 6-month group (P = 0.77). The median and interquartile ranges of the follow-up period were 11.7 months (6.0, 12.2) and 10.0 months (5.7, 12.1), for the 1-month group and 6-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 1-month group and in 16.0% of patients in the 6-month group (HR, 0.70; 95% CI, 0.33–1.47; P = 0.35) (Table 3 and Figure 2A). The major secondary composite endpoint occurred in 9.8% of patients in the 1-month group and 2.8% of patients in the 6-month group (HR, 3.00; 0.82–10.94; P = 0.096), with the difference explained mainly in terms of the higher incidence of non-cardiac death for the 1-month group (Table 3 and Figure 2B). There was no significant difference in the net clinical benefit of the 1-month and 6-month groups (10.8% vs. 5.7%; HR, 1.70; 95% CI, 0.63–4.61; P = 0.30) (Table 3 and Figure 2C).

Regarding the individual secondary endpoints, non-cardiac death was observed more frequently in the 1-month group than in the 6-month group (3.9% vs. 0%; P = 0.048); there were three cancer-related deaths and one pneumonia-related death. Stent

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thrombosis and myocardial infarction occurred in only one patient (in the 1-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).

DISCUSSION

The SAFE-A study was the first randomized trial comparing 1-month and 6-month of $P2Y_{12}$ inhibitor therapy, combined with aspirin and apixaban, for patients with AF who require coronary stenting. The major findings were that 1-month $P2Y_{12}$ inhibitor therapy was not superior to 6-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 ischemic coronary events between 1-month and 6-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 1-month group than in the 6-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

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(1-month) $P2Y_{12}$ inhibitor therapy for reducing bleeding complications. The lack of statistical significance was likely due to the limited number of enrolled patients. Although the study had originally aimed to enroll 600 patients (300 per group), enrollment was terminated after a sample size of 210 patients was reached. Slow enrollment was likely related to the physicians' concerns regarding the increased risk of bleeding associated with prolonged triple therapy.

The balance between the ischemic risk and bleeding risk is particularly important for patients who require anticoagulation or antiplatelet treatment. Regarding patients without AF, shorter (3–6 months) DAPT was associated with a significant reduction in major bleeding events, without increasing the risk of ischemic 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 randomized 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,

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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 ischemic events. The effect and safety of very early withdrawal of aspirin therapy (at 1–2 weeks) remain topics of debate because the first weeks after PCI are known to represent the period with the

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highest risk for coronary ischemic events. The AUGUSTUS trials did find a slightly smaller number of coronary ischemic 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 ischemic 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 suggested 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.

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Limitations

This study had several limitations. First, the number of enrolled patients was

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smaller than the target sample size established based on the original design because enrollment was slow and had to be terminated prematurely. Second, due to the open-label design, we could not exclude selection bias. However, the assessment 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 generalized 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 1-month group and 6-month group, respectively, which might have affected the results of the study.

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CONCLUSION

SAFE-A is the first randomized trial to compare 1-month and 6-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

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can reduce bleeding events after PCI for patients with AF.

Impact on Daily Practice

The SAFE-A is the first randomized trial to compare 1-month and 6-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 1 month after stenting. However, the results failed to show the superiority of such short-term $P2Y_{12}$ inhibitor treatment for reducing bleeding events, likely because of the inadequate statistical power.

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Acknowledgments

We thank Hiroyuki Hosokawa, Masahiro Sakai, Eriko Onose, and Koichi Hashimoto from the Tsukuba Clinical Research & Development Organization, University of Tsukuba, for their invaluable assistance with this study. We would like to thank Editage (www.editage.com) for English language editing.

Funding

This study was sponsored by grants from Bristol-Myers Squibb K.K.

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FIGURE LEGENDS

Figure 1: Study flow chart.

AF, atrial fibrillation.

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

BARC, Bleeding Academic Research Consortium

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Figure 3: Pre-specified subgroup analysis of the primary endpoint. Patients were stratified according to the duration of triple antithrombotic therapy (1-month group vs. 6-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 6-month group were used as a reference. CKD, chronic kidney disease.

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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
Dyslipidemia	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 enrollment			

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Aspirin	99 (99%)	103 (98%)	1.00
Apixaban			1.00
10 mg/day	64 (73%)	66 (73%)	
5 mg/day	24 (27%)	24 (27%)	
$P2Y_{12}$ inhibitor			0.48
Clopidogrel	55 (56%)	63 (61%)	
Prasugrel	44 (44%)	40 (39%)	
Antiulcer drug			0.51
Histamine type 2 receptor blocker	6 (7%)	9 (10%)	
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.

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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			0.74
Left anterior descending artery	48 (48%)	59 (56%)	
Left circumflex artery	21 (21%)	19 (18%)	
Right coronary artery	30 (30%)	26 (25%)	
Bypass graft	1 (1%)	1 (1%)	
Type of lesion			0.18
Type A	29 (29%)	17 (16%)	
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			0.084
1	89 (89%)	83 (80%)	
≥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).

PCI, percutaneous coronary intervention; IVUS, intra-vascular ultrasound; IABP, intra-aortic balloon pump.

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Table 3. Clinical outcomes

Outcome	Duration of $P2Y_{12}$ inhibitor					
	1 month (*n* = 102)		6 months (*n* = 106)		Hazard ratio (95% CI)	*P*-value
	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 embolization	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	11 (10.8%)	14.3	6 (5.7%)	7.9	1.70 (0.63, 4.61)	0.30

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infarction, stroke, or systemic embolization and bleeding complication (BARC type 3 or higher)						
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	-	-
Hospitalization 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 embolization	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 hospitalization 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, Thrombosis in Myocardial Infarction.

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Figure 1

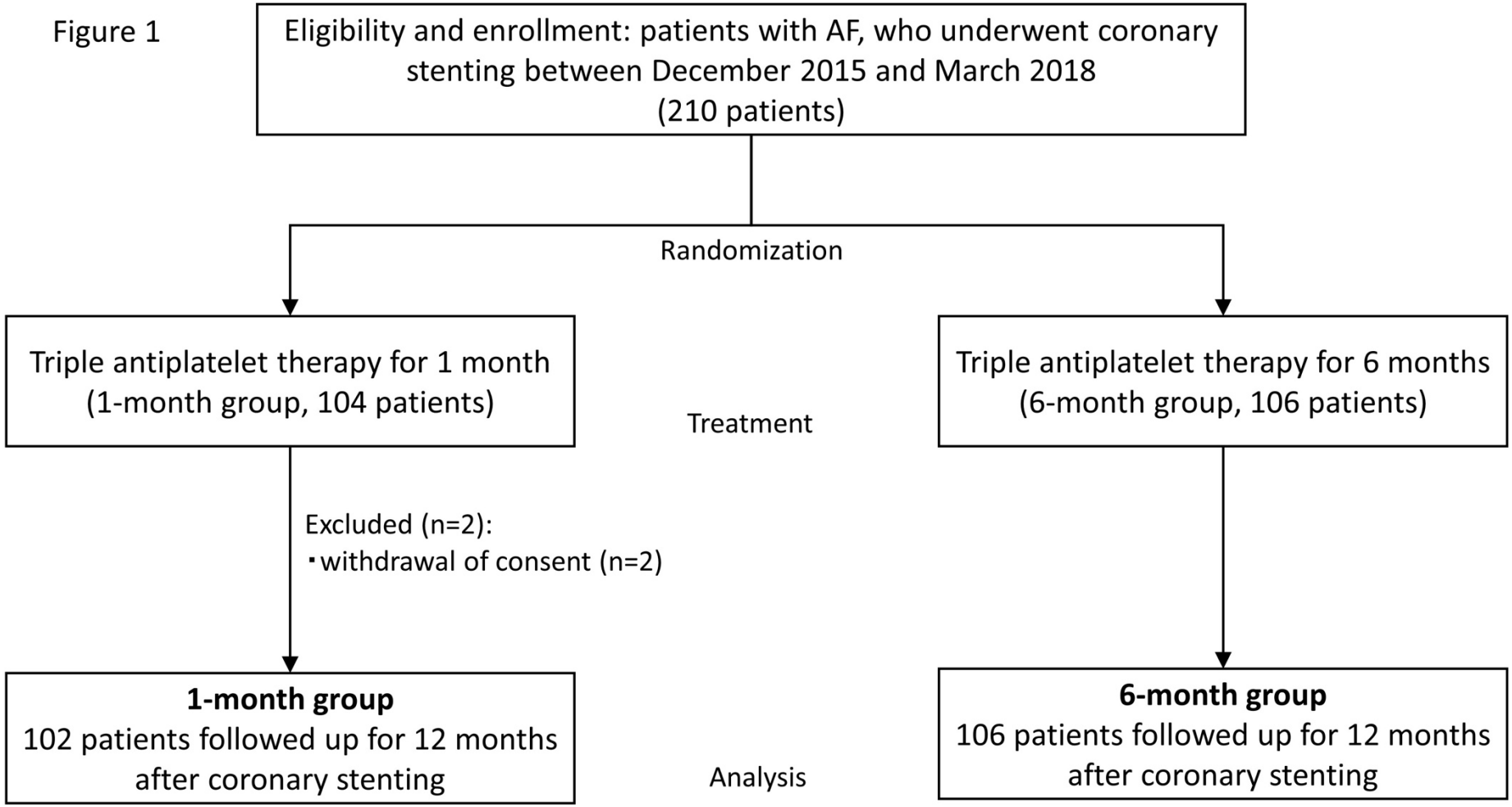

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Figure 2

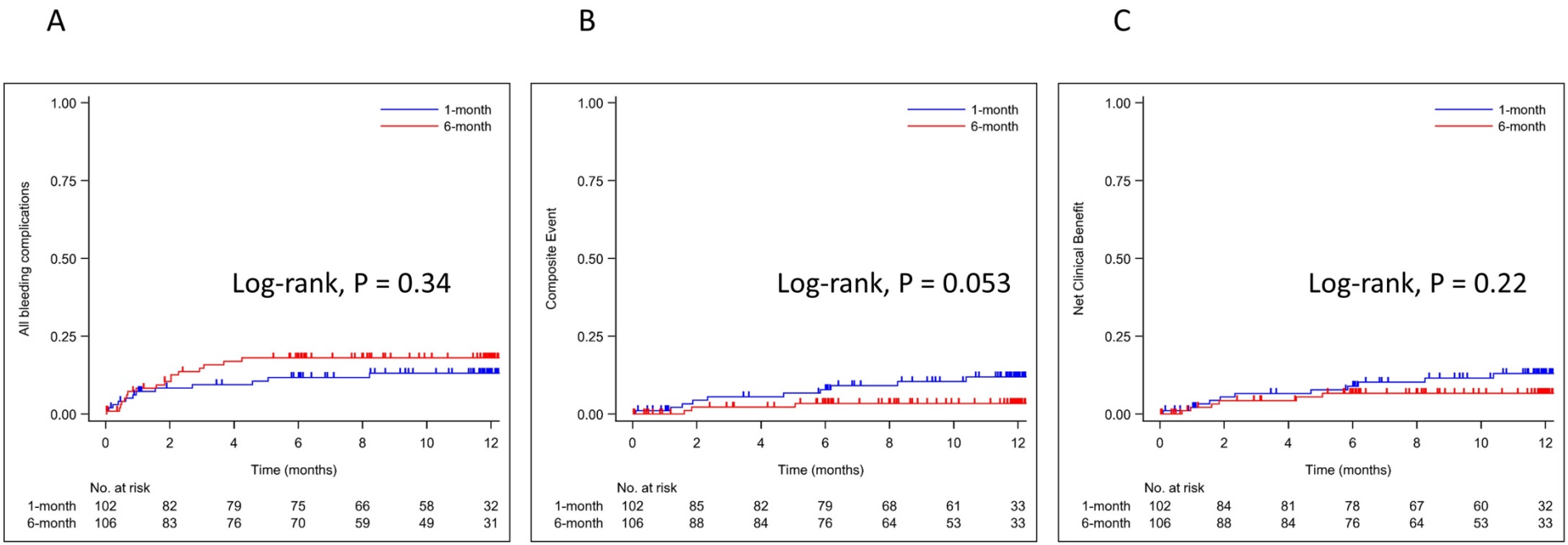

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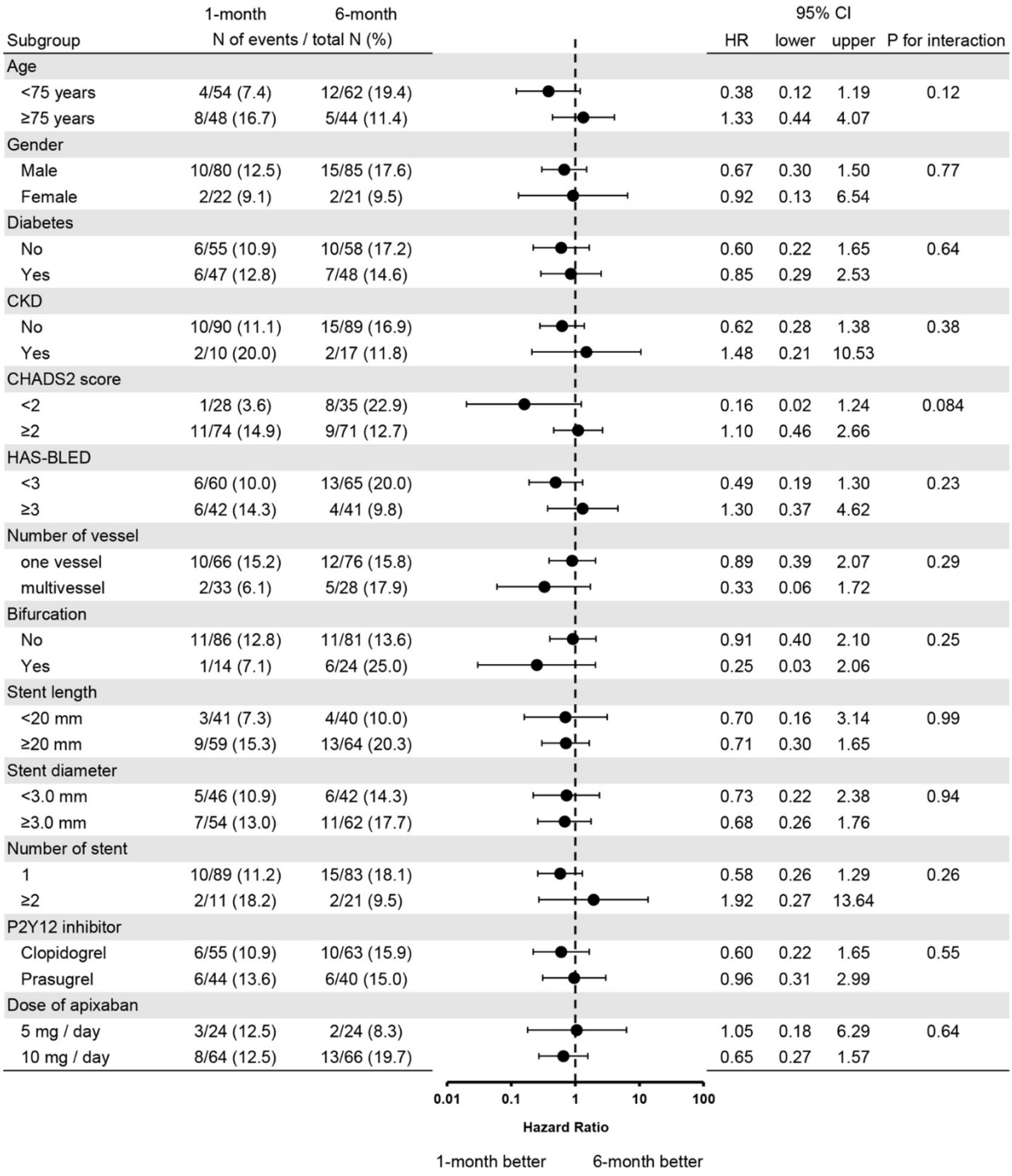
Figure 3



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Online Data Supplement

Supplemental Table 1: Definition of the Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria

Supplemental Table 2: Bleeding Academic Research Consortium (BARC) Definition for Bleeding

Supplemental Appendix: Study organization

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

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Supplemental Table 1. Definition of the Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria

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Major Bleeding

- Any symptomatic intracranial hemorrhage
- Clinically overt signs of hemorrhage (including imaging) associated with a drop in hemoglobin of ≥5 g/dL or a ≥15% absolute decrease in hematocrit)
- Fatal bleeding (bleeding that directory results in death within 7 days)

Minor Bleeding

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

Minimal bleeding

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

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Supplemental Table 2. Bleeding Academic Research Consortium (BARC) Definition for Bleeding

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Type 0: no bleeding

Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, 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 hemorrhage (eg, 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 nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3

Type 3a

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

Any transfusion with overt bleeding

Type 3b

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

Cardiac tamponade

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

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Bleeding requiring intravenous vasoactive agents

Type 3c

Intracranial hemorrhage (does not include microbleeds or hemorrhagic 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 h

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-h period †

Chest tube output 2L within a 24-h 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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CABG indicates coronary artery bypass graft. Platelet transfusion should not be included in these definitions.

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

† Cell saver products are not counted.

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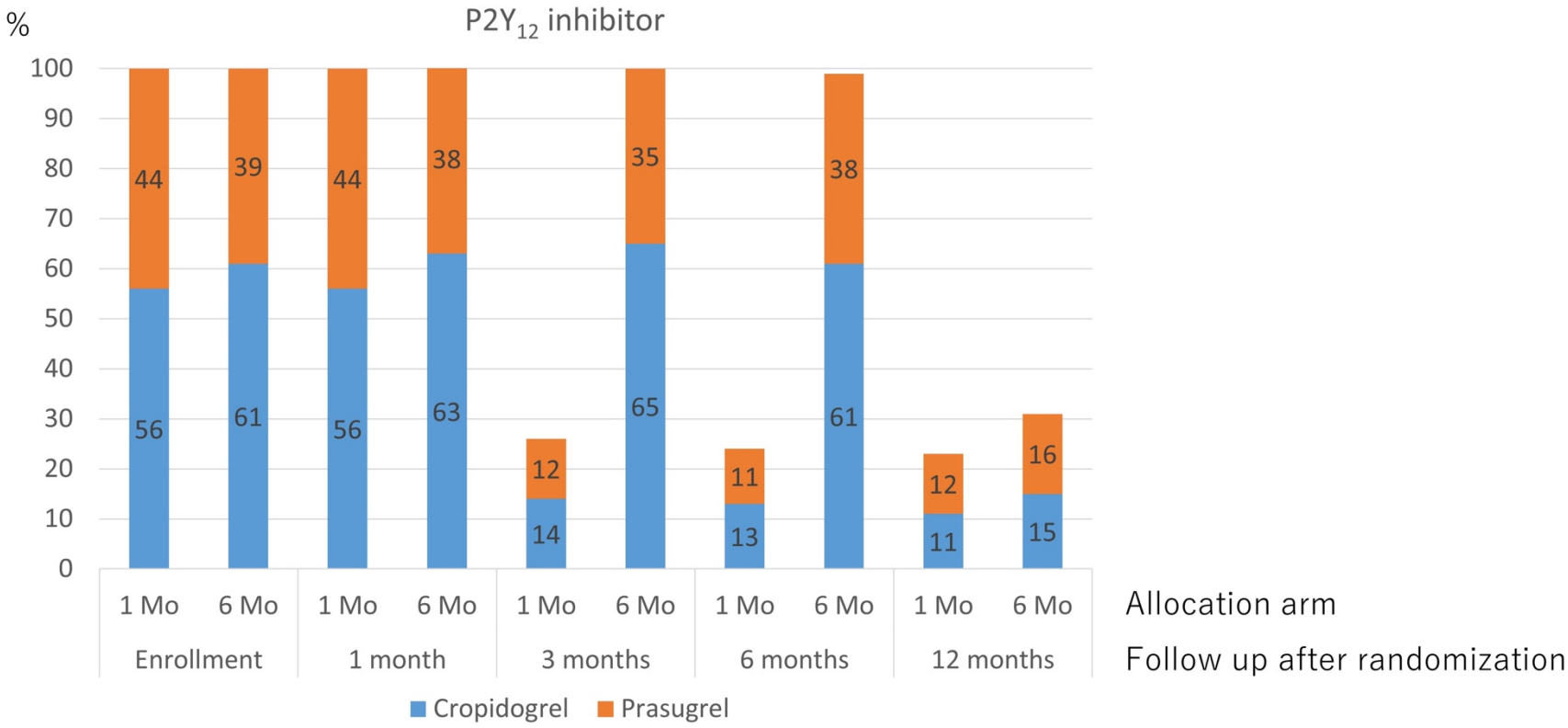
Supplemental Figure 1 A



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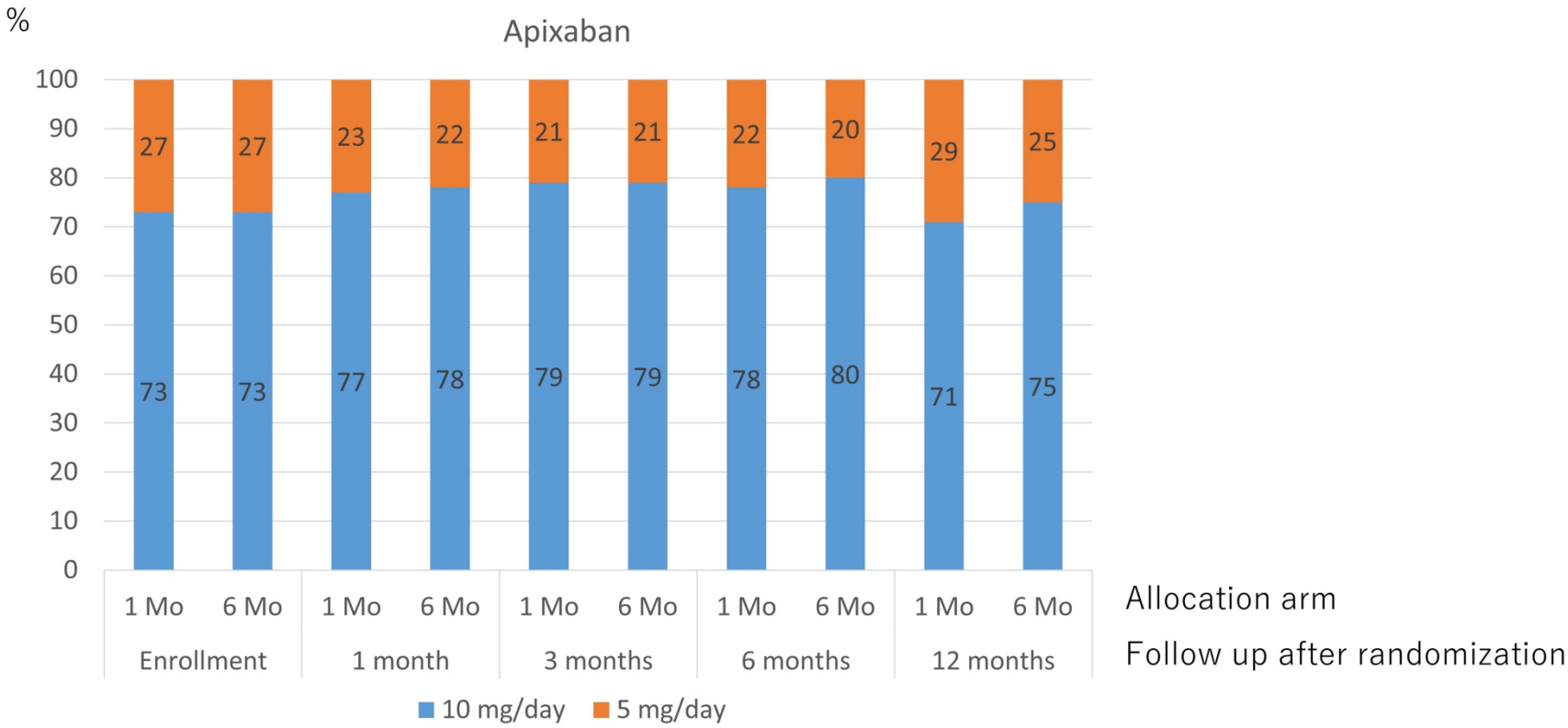
Supplemental Figure 1 B



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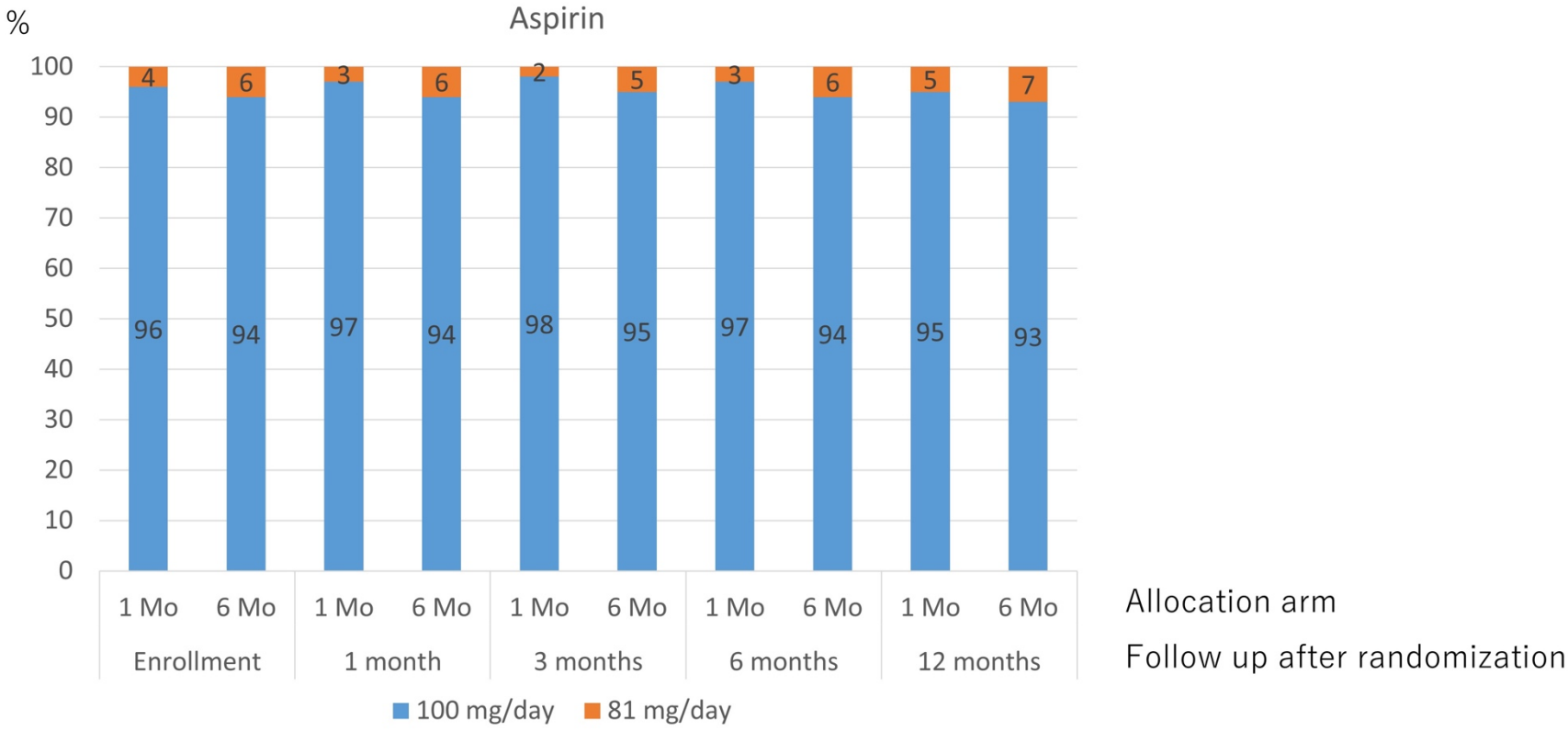
Supplemental Figure 1 C



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Supplemental Appendix. STUDY ORGANIZATION

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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

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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 Center, Data Center, and Quality Control

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

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3. Ibaraki Prefectural Central Hospital — Noriyuki Takeyasu
4. Ibaraki Seinan Medical Center Hospital — Hiroshi Maeda
5. Iwaki Kyoritsu Hospital — Masafumi Sugi

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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
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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
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38. Hitachinaka General Hospital	Takayoshi Yamanouchi
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