



## Randomized, Double-Blind Trial to Evaluate the Safety of Apixaban With Antiplatelet Therapy After Acute Coronary Syndrome in Japanese Patients (APPRAISE-J)

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**Background:** Concomitant anticoagulant therapy may further reduce the risk of thrombotic events in patients with acute coronary syndrome (ACS) when given in addition to current standard antiplatelet therapies. This Phase II, randomized, double-blind, placebo-controlled study in Japanese patients with ACS assessed the bleeding risk of apixaban compared with placebo when given in combination with standard antiplatelet therapy, and followed a similar design to APPRAISE-1, the larger global Phase II study.

**Methods and Results:** Patients with recently diagnosed ACS were randomized to receive apixaban 2.5 mg twice daily (BID; n=49), apixaban 5 mg BID (n=50), or placebo (n=52) in addition to standard antiplatelet therapy for 24 weeks. The composite primary endpoint of major or clinically relevant nonmajor bleeding occurred in 2 patients (4.1%) in each apixaban treatment group and 1 patient (2.0%) in the placebo group, and a dose-dependent increase was seen in all bleeding events. No hemorrhagic strokes occurred in either apixaban treatment group. This study was terminated before completion because the APPRAISE-2 global Phase III trial was stopped based on the recommendation of the Data Monitoring Committee, following an increase in bleeding events without a counterbalancing reduction in ischemic events.

**Conclusions:** The bleeding profile of apixaban in Japanese patients with ACS was similar to that found in the global APPRAISE-1 study, supporting the safety of apixaban in Japanese patients. (*Circ J* 2013; **77**: 2341–2348)

**Key Words:** Acute coronary syndrome; Apixaban; Factor Xa inhibitor; Japanese patients; Oral anticoagulant

Acute coronary syndrome (ACS), which includes both acute myocardial infarction (MI) and unstable angina (UA), is a leading cause of cardiovascular death worldwide. Although the rate of MI in Japan is lower than in countries such as the United States, MI still occurs in approximately 52 individuals per 100,000 per year,<sup>1</sup> with a reported recurrence rate of 1.5% per year.<sup>2</sup> Antiplatelet therapy, including aspirin, is a key component of therapy for ACS, and early administration is associated with significantly reduced mortality.<sup>3–5</sup>

has a known allergy or gastrointestinal hemorrhage.<sup>6,7</sup> Dual antiplatelet therapy (DAT), in which aspirin is used in combination with a thienopyridine, has been shown to further reduce the risk of both short- and long-term cardiovascular events.<sup>8,9</sup> Despite the available treatments, the risk of recurrent atherothrombotic events remains high in this patient population.<sup>8,9</sup> Combining an anticoagulant with DAT has been shown to reduce the risk of ischemic events, but also to increase the risk of serious bleeding events.<sup>10–12</sup>

Previous studies have demonstrated an increased risk of intracranial bleeding, relative to Caucasian patients, in ethnic Asian patients with atrial fibrillation (AF) when receiving similar strength warfarin anticoagulation therapy.<sup>13</sup> A recent analy-

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Guidelines recommend aspirin be given unless the patient

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sis of preliminary data from the ROCKET-AF trial of rivaroxaban in patients with AF provisionally identified a 2-fold increased risk of intracranial hemorrhage in Asian patients, compared with Caucasian patients, when treated with an anticoagulant.<sup>14</sup> By contrast, the Bleeding with Antithrombotic Therapy study identified an increase in bleeding risk associated with DAT in Japanese patients, but found no difference in bleeding rates between Japanese and Western patient populations when other factors were accounted for.<sup>15</sup> However, it is still unclear whether the rate of intracranial hemorrhage will be higher in Asian patients with the use of the new generation of oral anticoagulants.

Apixaban (BMS-562247) is a highly selective, potent, and orally bioavailable inhibitor of both free and prothrombinase-bound factor Xa.<sup>16,17</sup> Developed as a potential alternative anticoagulant to warfarin, apixaban does not require regular monitoring during routine clinical use owing to its wide therapeutic index, predictable pharmacokinetics, and limited potential for drug or food interactions.<sup>18,19</sup> In previous studies, apixaban pharmacokinetics and pharmacodynamics, as assessed by international normalized ratio, activated partial thromboplastin time, and modified prothrombin time, were found to be similar in Caucasian and Japanese subjects when matched by age, weight, and smoking status.<sup>18,20</sup> However, as with all anticoagulant therapy, the potential for bleeding remains a concern with this new agent.

The APPRAISE (Apixaban for Prevention of Acute Ischemic and Safety Events) series of studies have investigated the safety and efficacy of apixaban in patients with ACS. The initial global Phase II trial (APPRAISE-1) evaluated apixaban 2.5 mg twice daily (BID), 10 mg once daily (QD), 10 mg BID, or 20 mg QD as an add-on to standard antiplatelet therapy in 1,715 patients with ACS and 1 or more additional risk factors for stroke. The 20 mg QD and 10 mg BID doses were stopped on the recommendation of the Data and Safety Monitoring Committee (DSMC), owing to an excess of total bleeding events, and only the 2.5 mg BID and 10 mg QD doses were allowed to continue to the completion of the trial. APPRAISE-1 identified a trend towards a reduction in ischemic events, accompanied by a dose-related increase in bleeding risk with the addition of apixaban to antiplatelet therapy.<sup>21</sup> The subsequent global Phase III trial (APPRAISE-2) investigated apixaban 5 mg BID, comparing it with placebo when given in addition to standard antiplatelet therapy in 7,392 patients with a recent ACS and 2 or more additional risk factors for ischemic events.<sup>22</sup> However, the study was terminated prior to completion because of an observed increase in bleeding events without a counterbalancing reduction in ischemic events.

The APPRAISE-J study reported here was conducted at the same time as APPRAISE-2 and focused on Japanese patients with a recent (within 7 days) ACS and at least 2 additional risk factors for recurrent ischemic events, to evaluate the safety and bleeding profile of apixaban in this patient population when given in combination with standard antiplatelet therapy.

## Methods

### Study Participants

The study was intended to recruit 150 Japanese male and female patients aged  $\geq 20$  years within 7 days of the onset of ACS, with symptoms of myocardial ischemia lasting  $\geq 10$  min and one of troponin T or I, or creatinine kinase-MB above the upper limit of normal or ST deviation  $>0.1$  mV (1.0 mm). Patients were required to be clinically stable and receiving stan-

dard antiplatelet therapy (aspirin  $\leq 100$  mg/day, with or without clopidogrel 75 mg/day or ticlopidine 200 mg/day, based on their physician's judgment), with 2 or more of the following additional risk factors for recurrent ischemic events: age  $\geq 65$  years, elevated cardiac markers and ST deviation  $>0.1$  mV, diabetes mellitus, cerebrovascular disease, peripheral vascular disease, heart failure or left ventricular ejection fraction  $\leq 40\%$ , nonrevascularized multivessel coronary artery disease ( $\geq 2$  vessels), or mild-to-moderate renal insufficiency (creatinine clearance [CLcr] 30–90 ml/min). All patients were required to provide written informed consent prior to screening in order to participate in the study.

Key exclusion criteria were: any clear bleeding event or if a patient was considered at high risk of bleeding; any tendency or suspected hereditary disposition to thrombus formation; severe renal impairment (CLcr  $<30$  ml/min); severe hepatic disorder; severe heart failure (New York Heart Association grade IV); treatment-resistant hypertension or severe hypertension (systolic  $\geq 180$  mmHg or diastolic  $\geq 110$  mmHg) during the observation period; thrombocytopenia (platelet count  $<100,000/\text{mm}^3$ ); or any severe, progressive, or uncontrollable condition determined by the investigator to be a risk for participation in the trial. Patients were also excluded from participating if they had received any investigational compound within 4 weeks prior to the study, required continuation of anticoagulant therapy, were receiving chronic therapy with nonsteroidal anti-inflammatory drugs or aspirin  $>100$  mg/day during the trial, or if they were considered unsuitable for aspirin therapy because of allergy or intolerance. Female patients were also excluded if they were pregnant, breastfeeding, or tested positive on a pregnancy test at enrollment or at the start of study treatment. Women of child-bearing age were required to use effective birth control for the duration of the study.

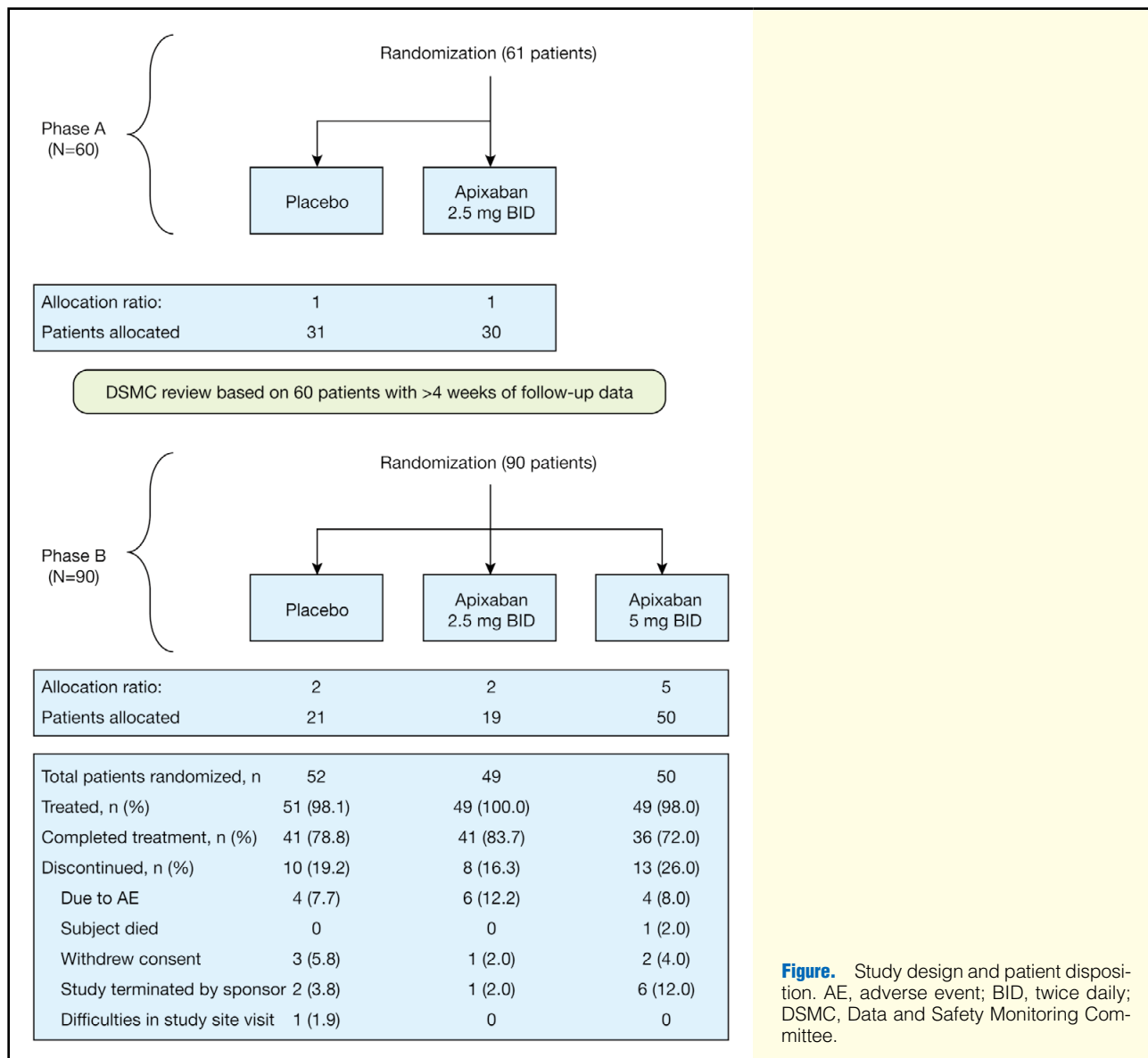
### Study Design

APPRAISE-J (NCT00852397) was a Phase II, placebo-controlled, randomized, double-blind, 24-week, multicenter study to evaluate the bleeding profile of apixaban 2.5 mg or 5 mg BID in combination with standard antiplatelet therapy (aspirin or aspirin+thienopyridine), in Japanese patients with recent ( $\leq 7$  days) ACS.

A summary of the study design is shown in the [Figure](#). The study planned to recruit a total of 150 patients at 20 sites over 2 phases, with patients initially randomly assigned to only the lower 2.5 mg BID dose of apixaban or placebo in a 1:1 ratio (phase A). After the first 60 patients had been recruited in phase A, patient registration was to be suspended pending completion of a safety review by the DSMC when all patients had undergone 4 weeks or more of study treatment. Subject to the results of the safety review, registration would recommence with patients in phase B randomly assigned to receive placebo, apixaban 2.5 mg BID, or apixaban 5 mg BID in a 2:2:5 ratio, such that the final ratio of patients in each treatment arm would be 1:1:1. A second safety review was to be carried out when 30 patients assigned to the 5 mg BID dose of apixaban had completed 4 weeks of treatment.

Randomization was carried out using a computer-generated, randomized, block design, stratified by the use of concomitant thienopyridine (clopidogrel or ticlopidine) antiplatelet therapy. All patients and investigators or other personnel involved in the study were blinded with respect to study treatment until the end of the trial (unblinded data were available to the DSMC in a closed fashion), with blinding only broken in the event of an emergency.

The protocol for the study was approved by the ethics com-



mittees of all institutions that participated in the study and it complied with all local regulations, the Declaration of Helsinki, and the International Conference on Harmonisation Guideline for Good Clinical Practice.

### Study Endpoints

The primary endpoint was a composite of International Society on Thrombosis and Haemostasis (ISTH)-defined major<sup>23</sup> and clinically relevant nonmajor (CRNM) bleeding (defined as acute or subacute clinically overt bleeding that does not satisfy the criteria for major bleeding, and that leads to hospital admission for bleeding, physician-guided medical or surgical treatment for bleeding, or a change in antithrombotic therapy) events during the treatment period. Secondary bleeding endpoints were the safety of apixaban with respect to major bleeding events, minor bleeding events, and all bleeding events. Other secondary endpoints included the safety and efficacy of apixaban with respect to cerebrocardiovascular events (including all deaths, nonfatal MI, UA, and stroke), as well as the safety and tolerability of apixaban with respect to all adverse

events (AEs) or abnormal changes in laboratory test results.

### AE Monitoring and Laboratory Analyses

AEs were identified by spontaneous reporting, elicited during medical interviews using non-leading questions. Events were categorized by preferred term and system organ class according to the Medical Dictionary for Regulatory Activities definitions. In each case, the dates of onset and resolution, severity, seriousness, causal relationship with the study treatment, and any action taken were recorded. Laboratory evaluations of hematology, clinical chemistry, and urinalysis were carried out pre-dosing and at weeks 4, 8, 16, and 24.

### Statistical Methods

The target sample size of 150 patients was determined based on the results of the APPRAISE-1 global Phase II ACS study.<sup>21</sup> Assuming that the incidence of the composite of ISTH-defined major or CRNM bleeding for Japanese subjects is 3.0% in the placebo group and ranges from 5.7% to 7.9% in the apixaban groups, this sample size provides the precision of

**Table 1. Patients' Demographics and Baseline Characteristics**

	Placebo (n=52)	Apixaban 2.5 mg BID (n=49)	Apixaban 5 mg BID (n=50)	Total (n=151)
Age, years (SD)	63.9 (10.1)	66.0 (9.0)	64.0 (9.2)	64.6 (9.5)
Sex, n (%)				
Male	42 (80.8)	43 (87.8)	46 (92.0)	131 (86.8)
Female	10 (19.2)	6 (12.2)	4 (8.0)	20 (13.2)
Weight, kg (SD)	64.5 (12.1)	66.5 (10.2)	65.6 (11.4)	65.5 (11.2)
BMI, kg/m <sup>2</sup> (SD)	24.5 (3.2)	24.8 (3.4)	24.3 (2.9)	24.5 (3.1)
Index event, n (%)				
STEMI	41 (78.8)	35 (71.4)	38 (76.0)	114 (75.5)
Non-STEMI	5 (9.6)	7 (14.3)	11 (22.0)	23 (15.2)
UA	6 (11.5)	7 (14.3)	1 (2.0)	14 (9.3)
Additional risk factors, n (%)				
2	17 (32.7)	17 (34.7)	16 (32.0)	50 (33.1)
3	23 (44.2)	17 (34.7)	19 (38.0)	59 (39.1)
≥4	12 (23.1)	15 (30.6)	15 (30.0)	42 (27.8)
Age ≥65 years	25 (48.1)	31 (63.3)	28 (56.0)	84 (55.6)
Dynamic ST deviation and elevated cardiac markers	44 (84.6)	40 (81.6)	44 (88.0)	128 (84.8)
Diabetes mellitus	26 (50.0)	18 (36.7)	16 (32.0)	60 (39.7)
MI within 12 months	1 (1.9)	0	0	1 (0.7)
Cerebrovascular disease	0	4 (8.2)	2 (4.0)	6 (4.0)
Peripheral vascular disease	1 (1.9)	0	1 (2.0)	2 (1.3)
Prior symptomatic CHF or LVEF ≤40%	4 (7.7)	3 (6.1)	7 (14.0)	14 (9.3)
Nonrevascularized multivessel CAD (≥2 vessels)	28 (53.8)	28 (57.1)	23 (46.0)	79 (52.3)
Mild or moderate renal insufficiency	29 (55.8)	28 (57.1)	32 (64.0)	89 (58.9)
PCI, n (%)	51 (98.1)	49 (100.0)	50 (100)	150 (99.3)
Concomitant antiplatelet therapy, n (%)				
Mono	2 (3.8)	0	2 (4.0)	4 (2.6)
Dual	50 (96.2)	49 (100.0)	48 (96.0)	147 (97.4)

BID, twice daily; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

8–9% for the half-length of the 95% confidence intervals (CIs) for the difference of proportions between each apixaban dose group and the placebo group. In addition, assuming that the true incidence of the composite of major or CRNM bleeding events is 5.7% in the apixaban groups, this sample size could detect more than 1 bleeding event with a probability of approximately 95%.

The safety analysis set included data from all patients who had received at least 1 dose of study medication (including placebo). All safety analyses were based on the safety analysis set. The efficacy analysis set included data from all patients randomized to treatment over the treatment period. Bleeding, MI, UA, stroke, and cause of death were confirmed by the Clinical Event Committee; the final analysis included only events confirmed by adjudication.

The 2-sided 95% CI values for single binomial proportions were calculated based on the Clopper-Pearson method, and the 95% CI values for the difference between 2 binomial proportions were calculated using the Chan-Zang method; both methods were implemented within SAS® version 8.2 (SAS Institute Inc, Cary, NC, USA) and/or Proc-StatXact version 5.0 (Cytel Inc, Cambridge, MA, USA). Incidence rates were calculated as the number of patients with “event” divided by total number of patient-days at risk. Because of the relatively small number of patients per group and the low expected number of bleeding and efficacy events, no formal statistical

testing was conducted. Therefore, 2-sided 95% CIs are provided; P values were not calculated for the study endpoints and no subanalysis was conducted for each phase.

## Results

The first patient was enrolled in the APPRAISE-J study on April 8, 2009. Based on the DSMC safety review, which analyzed data from 61 patients enrolled during the initial phase of the study, a recommendation was made to continue with the second phase of the study, including randomly assigning patients to the higher 5 mg BID apixaban treatment group. The APPRAISE-J study was terminated on November 19, 2010, prior to all patients completing the study on the recommendation of the DSMC for the concurrent APPRAISE-2 global ACS trial, which had identified an excess of bleeding events that was not offset by a meaningful reduction in ischemic events in patients receiving apixaban in APPRAISE-2. The decision to terminate APPRAISE-J early was not related to the results observed in the study itself. However, at the time of termination, the intended number of patients had already been enrolled and all but 9 patients had completed the study.

### Patient Disposition and Baseline Characteristics

Over the course of the study, 151 patients were randomly assigned to treatment; of these, 1 patient in the placebo group and

**Table 2. Summary of Bleeding Events**

	Placebo (n=51)	Apixaban 2.5 mg BID (n=49)	Apixaban 5 mg BID (n=49)	All apixaban (n=98)
ISTH bleeding endpoints				
ISTH major or CRNM bleeding	1 (2.0) [0.10–9.82]	2 (4.1) [0.73–13.34]	2 (4.1) [0.73–13.34]	4 (4.1) [1.41–9.63]
ISTH major bleeding	0 [0.00–6.31]	1 (2.0) [0.10–10.24]	2 (4.1) [0.73–13.34]	3 (3.1) [0.84–8.15]
CRNM bleeding	1 (2.0) [0.10–9.82]	1 (2.0) [0.10–10.24]	0 [0.00–6.53]	1 (1.0) [0.05–5.02]
Minor bleeding	16 (31.4) [19.63–45.07]	18 (36.7) [23.64–51.64]	20 (40.8) [27.00–55.79]	38 (38.8) [29.10–48.79]
All bleeding	17 (33.3) [20.76–47.23]	19 (38.8) [26.01–53.76]	22 (44.9) [30.83–59.77]	41 (41.8) [31.95–52.23]
Total patient-days exposure	6,012	5,936	5,132	11,068
Incidence rate/100 patient-days	0.283	0.320	0.429	0.370

All data are presented for number (%) of patients, with 95% confidence intervals. BID, twice daily; CRNM, clinically relevant non-major; ISTH, International Society on Thrombosis and Haemostasis.

**Table 3. Summary of All AEs**

	Placebo (n=51)	Apixaban 2.5 mg BID (n=49)	Apixaban 5 mg BID (n=49)	Any apixaban (n=98)
AEs, n				
All-causality	116	108	97	205
Treatment-related	24	15	23	38
Patients with AEs, n (%)				
All-causality	44 (86.3)	40 (81.6)	38 (77.6)	78 (79.6)
Treatment-related	16 (31.4)	13 (26.5)	19 (38.8)	32 (32.7)
Patients with serious AEs,* n (%)				
All-causality	8 (15.7)	11 (22.4)	7 (14.3)	18 (18.4)
Treatment-related	1 (2.0)	2 (4.1)	3 (6.1)	5 (5.1)
Patients with severe or very serious AEs, n (%)				
All-causality	2 (3.9)	1 (2.0)	2 (4.1)	3 (3.1)
Treatment-related	0	0	2 (4.1)	2 (2.0)
Patients discontinued because of AEs, n (%)				
All-causality	4 (7.8)	6 (12.2)	5 (10.2)	11 (11.2)
Treatment-related	2 (3.9)	1 (2.0)	5 (10.2)	6 (6.1)
Patients with temporary discontinuation because of AEs, n (%)				
All-causality	4 (7.8)	3 (6.1)	1 (2.0)	4 (4.1)
Treatment-related	2 (3.9)	0	1 (2.0)	1 (1.0)

\*Includes all serious AEs reported in this study. AE, adverse event; BID, twice daily.

1 in the apixaban 5 mg BID group did not receive any study treatment. A total of 31 patients withdrew from the study prior to completion, with 118 (78.1%) patients completing the study. A summary of patient disposition is shown in [Figure](#).

All of the 151 patients randomly assigned to treatment were Japanese, with a mean (range) age of 64.6 (34–81) years. No obvious differences were seen with respect to demographic or baseline characteristics among all treatment groups and the additional risk factors for stroke identified at baseline were similar among treatment groups ([Table 1](#)). Although the intention of this study was to recruit a high-risk patient population with at least 2 additional risk factors for recurrent ischemic events, approximately 28% of all patients enrolled in the study had 4 or more additional risk factors. Approximately 40% of patients enrolled had diabetes mellitus, almost 60% had renal insufficiency, all but 4 of the patients in the study (97.4%) were receiving DAT at baseline, and all but 1 patient had undergone percutaneous coronary intervention (PCI; 99.3%).

### Bleeding Endpoints

The composite primary endpoint of major or CRNM bleeding

occurred in 1 patient (2.0%) in the placebo group and in 2 patients (4.1%) in each of the apixaban treatment groups. A trend towards a dose-dependent increase was seen in all bleeding events, with 17 (33.3%), 19 (38.8%), and 22 (44.9%) patients with reported events in the placebo, apixaban 2.5 mg BID, and apixaban 5 mg BID groups, respectively. A summary of all bleeding events is shown in [Table 2](#) and details of the most frequent bleeding-related events are shown in [Table S1](#).

### Efficacy Endpoints

One patient in the placebo group experienced a nonhemorrhagic stroke (lacunar stroke) on day 35 of the study, considered unrelated to the study treatment. One patient in the apixaban 5 mg BID group experienced cardiorespiratory arrest resulting in death on day 4 after study treatment commenced and was considered related to study treatment. There were no deaths, nonhemorrhagic strokes, MIs, or cases of UA during the study for any patients in the apixaban 2.5 mg BID group. A summary of efficacy events is shown in [Table S2](#).



## AEs and Liver Function

There were no clinically meaningful differences between treatment groups in the incidence of all-causality AEs, treatment-related AEs, serious AEs, or discontinuations because of AEs. A summary of AEs that occurred during the treatment period is shown in Table 3.

Most AEs were mild or moderate in severity, with 26 serious AEs observed, including 1 serious AE with an outcome of sudden cardiac death in the apixaban 5 mg BID group that was considered related to study treatment. All of the AEs that resulted in permanent discontinuation of treatment and most of the AEs that resulted in temporary discontinuation were unique to the patients in which they occurred. No abnormal elevations of aspartate transaminase (AST), alanine transaminase (ALT), or total bilirubin levels were observed in any of the treatment groups.

## Discussion

APPRAISE-J set out to evaluate the bleeding profile of apixaban 2.5 mg and 5 mg BID in combination with standard antiplatelet therapy in Japanese patients with recent ( $\leq 7$  days) ACS. The study was stopped prior to completion in response to a safety signal seen in the larger global APPRAISE-2 study that was running simultaneously,<sup>22</sup> despite the absence of any particular safety concerns observed in APPRAISE-J. At study termination, the planned number of patients had already been enrolled and only 9 patients had yet to complete the study. As the number of subjects terminated from the study prior to completion was small, the efficacy and safety evaluation in this study was not significantly affected.

ISTH major or CRNM bleeding events occurred in 2 patients (4.1%) in both apixaban groups and in 1 patient (2.0%) in the placebo group. The incidence of all bleeding events was greater in the apixaban groups than in the placebo group, with a trend towards a dose-dependent increase in all bleeding events observed with apixaban in APPRAISE-J, as was seen in the APPRAISE-1 Phase II study.<sup>21</sup> Importantly, however, the incidence of clinically significant bleeding events such as ISTH major or CRNM bleeding was similar across the different dosing groups. APPRAISE-J was performed in 2 phases, with only the lower apixaban dose in phase A and the higher dose included in phase B, owing to concern that the incidence of bleeding in Japanese patients may be higher than previously seen in Western patients. However, a comparison with the results of the APPRAISE-1 Phase II study identified no increase in major or CRNM bleeding events specific to Japanese patients, supporting the safety of apixaban in Japanese patients.

There were no cases of hemorrhagic stroke reported in either of the apixaban treatment groups. No indications of hepatotoxicity and no abnormal elevations of AST, ALT, or total bilirubin levels were observed in any treatment group, and apixaban was generally safe and well tolerated within this Japanese patient population.

Other studies have observed differences in bleeding and stroke risk between Japanese patients and patients enrolled in most Phase III clinical trials, who are primarily Caucasian. Although the exact cause of these differences remains unknown, registry studies such as Reduction of Atherothrombosis for Continuous Health (REACH)<sup>24</sup> have identified a distinct prevalence of comorbidities in Japanese patients compared with those seen in North American and European patient populations, such as a higher rate of cardiovascular disease in relation to coronary artery disease. In addition, there are also some

notable differences in the therapies recommended for treatment of patients with ACS in Japan vs. the United States/Europe.<sup>7,25</sup> An example of this are glycoprotein IIb/IIIa inhibitors, which are used in the United States and Europe but are not currently approved for use in Japan.

By design, APPRAISE-2 and APPRAISE-J enrolled unique populations of high-risk patients, requiring at least 2 additional risk factors for eligibility. Over 50% of the patients in APPRAISE-J and APPRAISE-2 had 3 or more additional risk factors, and over one-quarter of patients in APPRAISE-J had as many as 4 or more additional risk factors. A substantially greater proportion of patients in APPRAISE-J had undergone PCI (99.3% compared with ~44% of patients in APPRAISE-2) and a higher proportion of patients were receiving concomitant DAT (97.4% compared with 81% in APPRAISE-2). As these factors and concomitant therapies are also known risk factors for bleeding, the patient populations for these studies could be expected to have a higher risk of bleeding than the populations enrolled in other studies of patients with ACS.

The results of the APPRAISE series of studies demonstrate the challenges involved in adding anticoagulant therapy to DAT in a high-risk population of patients with ACS and, together with other studies, indicate a need for caution when giving triple therapy to patients with ACS.<sup>10-12,21,22</sup> However, the results of the ATLAS-TIMI 51 ACS-2 trial, in which rivaroxaban, also an oral direct factor Xa inhibitor, was compared with placebo when given in addition to antiplatelet therapy in patients with ACS, indicate that there may be a subpopulation of patients who benefit from the addition of anticoagulant to DAT.<sup>26</sup>

The recent European Society of Cardiology position paper by De Caterina et al identified several potential reasons for the differences between the ATLAS-TIMI ACS 51 results and those of APPRAISE-2, citing the higher-risk population included in APPRAISE-2, which had a higher incidence of MI vs. UA and of non-ST-elevation MI vs. ST-elevation MI.<sup>27</sup> The commentary also noted the difference in factor Xa inhibition potency used in the 2 trials, with APPRAISE-2 using the same dose (5 mg BID) as used in AF, and ATLAS-TIMI ACS 51 using only one-quarter to one-fifth (2.5–5 mg QD) of the dose used in AF. Despite this, De Caterina et al note that the incidence of bleeding was increased to a similar extent in both trials, and that the efficacy gain for rivaroxaban was greater in the later rather than the earlier part of the study. They concluded that early termination of APPRAISE-2 may, therefore, have resulted in a greater effect of chance, and that the wide 95% CIs for efficacy from APPRAISE-2 do not exclude a remaining potential for a reduction in ischemic rates.

The APPRAISE-J study was not powered to study efficacy events and no conclusions regarding efficacy should be drawn. However, a numerical improvement in the efficacy and safety results was seen with the lower 2.5 mg dose, compared with the 5 mg dose. As demonstrated in the ATLAS-TIMI 51 trial,<sup>26</sup> excess bleeding was noted even with the addition of a lower dose of rivaroxaban than was tested in AF. This implies that the appropriate dose for the ACS patients, most of whom are treated with DAT, should be lower than that for AF patients not receiving any additional antiplatelet therapy.

The current JCS guidelines recommend concomitant warfarin and antiplatelet therapy for prevention of secondary cardiovascular events after MI in patients with AF.<sup>28</sup> However, the exclusion criteria of the APPRAISE-J study reported here prevented enrollment of patients who required continuous anticoagulant therapy, and thus excluded patients with AF requiring warfarin therapy; the risks and benefits of apixaban in pa-

tients with both AF and ACS were not addressed. Apixaban is effective for stroke prevention in patients with AF, compared with dose-adjusted warfarin (target international normalized ratio, 2–3), and is associated with significantly lower bleeding risk.<sup>29,30</sup> However, the balance between the increased bleeding risks associated with apixaban and concomitant antiplatelet therapy in patients with both ACS and AF and any increased protection from thrombotic events, has yet to be determined. Therefore, further study would be required to evaluate the potential use of apixaban in place of warfarin for this patient subgroup.

In conclusion, both apixaban treatments (2.5 mg and 5 mg BID) were generally safe and well tolerated in this patient population. The bleeding profile seen in Japanese patients was similar to that of the global APPRAISE-1 study, supporting the safety of apixaban in Japanese patients. The benefit-risk balance of anticoagulant therapy combined with antiplatelet therapy in patients with ACS and AF may be different from that for either indication alone, and further studies are necessary to draw a conclusion.

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## Appendix

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## Supplementary Files

### Supplementary File 1

**Table S1.** Bleeding-Related Adverse Events by MedDRA Version 13.1 System Organ Class and Preferred Term

**Table S2.** Summary of Efficacy Events

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