



# Safety and Efficacy of the Oral Direct Factor Xa Inhibitor Apixaban in Japanese Patients With Non-Valvular Atrial Fibrillation

– The ARISTOTLE-J Study –

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**Background:** Guidelines recommend warfarin as the standard of care for patients with atrial fibrillation (AF) at moderate or high risk for stroke. This phase II study assessed the effects of 2 doses of the factor Xa inhibitor apixaban vs. warfarin in Japanese patients with non-valvular AF. The composite primary endpoint was major and clinically relevant non-major (CRNM) bleeding.

**Methods and Results:** Two hundred and twenty-two patients with AF and 1 or more additional risk factors for stroke were randomized (1:1:1) to double-blind apixaban 2.5 or 5 mg b.i.d. or open-label warfarin (target international normalized ratio 2.0–3.0; 2.0–2.6 if age  $\geq$ 70 years) for 12 weeks. The primary endpoint occurred in 1 patient (1.4%) in each apixaban group and 4 (5.3%) warfarin patients. There were no strokes, systemic emboli, myocardial infarctions, or deaths in either apixaban group. The warfarin group had 2 ischemic strokes and 1 subarachnoid hemorrhage, but there were no deaths. Major and CRNM bleeds each occurred with higher frequency in the warfarin group vs. either apixaban group. Most adverse events were mild or moderate. No patients had hepatic aminotransferase elevations greater than 3 times the upper limit of normal.

**Conclusions:** In Japanese patients with AF, apixaban 2.5 and 5 mg b.i.d. were well tolerated over 12 weeks. A global phase III trial, which includes Japanese patients, is ongoing (ClinicalTrials.gov Identifier NCT00787150). (*Circ J* 2011; **75**: 1852–1859)

**Key Words:** Apixaban; Japanese patients; Non-valvular atrial fibrillation; Oral anticoagulant

Non-valvular atrial fibrillation (AF) is a common arrhythmia in Europe, North America, and Japan. AF affects approximately 1% of the general population in Western countries and 0.6% in Japan, with the prevalence increasing significantly with age over 60 years.<sup>1,2</sup> The risk for stroke is 3- to 5-fold higher in people who have AF than in those without AF in Western and Japanese populations,<sup>3,4</sup> and increases from 1.5% in AF patients at age 50–59 to 23.5% among those aged  $\geq$ 80 years.<sup>4</sup>

recommend them for reduction of stroke risk in AF patients at moderate to high risk of stroke,<sup>6–10</sup> they are contraindicated in many patients and often underutilized even in eligible patients for whom they are indicated.<sup>11–13</sup> Warfarin has numerous food and drug interactions, a relatively narrow therapeutic window, increased risk of bleeding, and the requirement for frequent monitoring and dose adjustments. Acetylsalicylic acid (ASA) has been recommended for AF patients at lower risk of stroke, but is less effective than warfarin.<sup>6,7</sup> In fact, the Japan AF Stroke trial found ASA to be neither effective nor safe; hence, it is not recommended in Japanese guidelines.<sup>10,14</sup>

In the search for efficacious, safe, well tolerated, and convenient alternatives to current anticoagulants for stroke

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Although vitamin K antagonists such as warfarin reduce the stroke risk in AF by as much as 60%,<sup>5</sup> and guidelines

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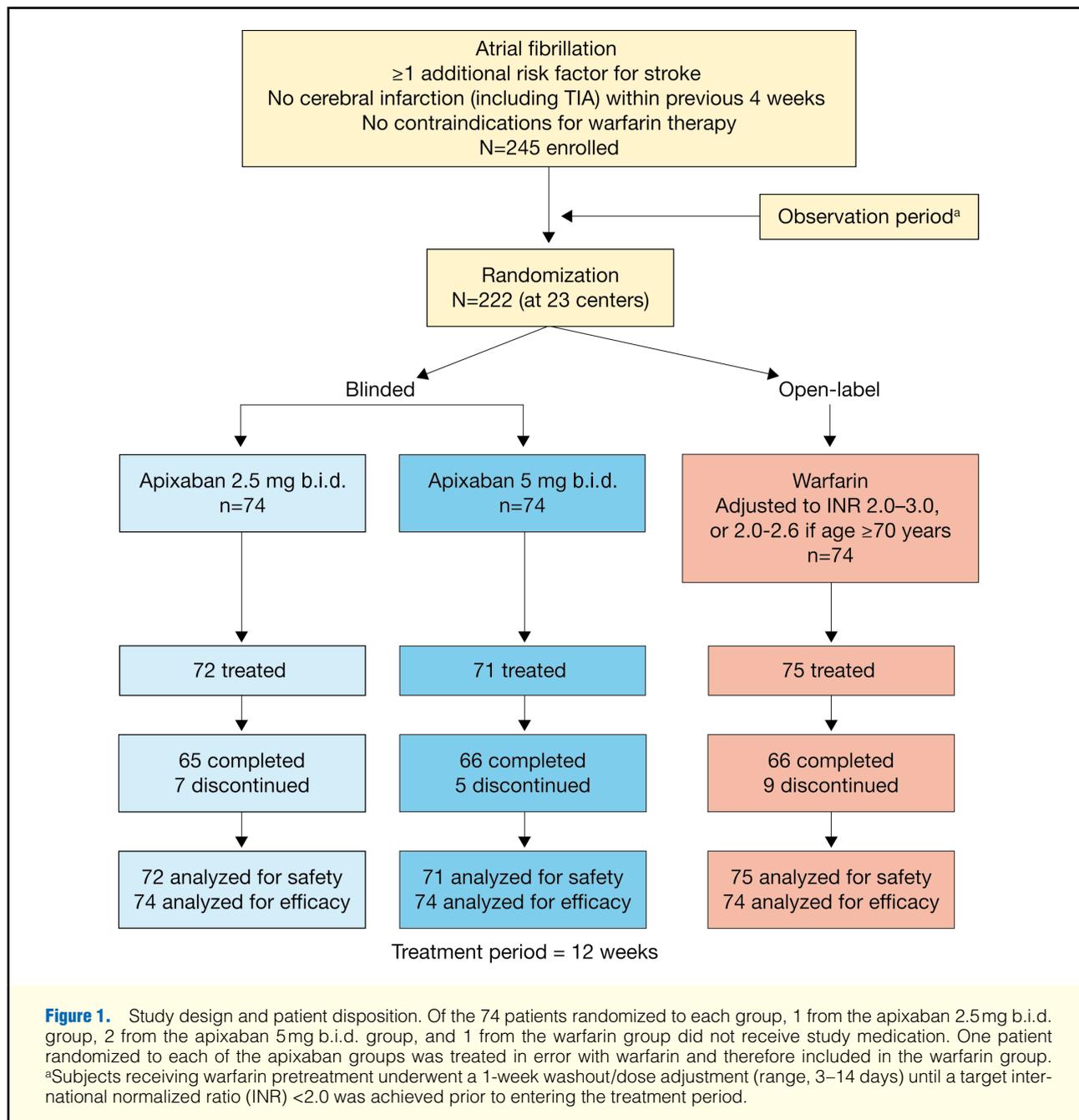
ARISTOTLE-J Study Group members listed in the Appendix.

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prevention in non-valvular AF, several novel oral agents that are either direct thrombin or factor Xa inhibitors are under development.<sup>15–19</sup> Apixaban, a potent, oral, reversible, direct, and highly selective factor Xa inhibitor, has a predictable pharmacokinetic and pharmacodynamic profile, does not require routine monitoring, is not affected by food intake, and has limited drug interactions.<sup>20–25</sup> It has rapid absorption and a half-life of approximately 12 h.<sup>26</sup> Apixaban exposure was similar in Japanese and Caucasian subjects matched for weight, age, and smoking status.<sup>27</sup> The ongoing phase III program for apixaban for stroke prevention in patients with non-valvular AF<sup>28,29</sup> includes the ARISTOTLE trial, which is comparing apixaban with warfarin in >18,000 patients, and the AVERROES trial, which is comparing apixaban with aspirin in 5,600 patients. Recently, it was announced that the

AVERROES trial has been stopped early because of clear evidence of a significant benefit of apixaban compared with aspirin with no significant difference in the risk of major bleeding.<sup>30</sup>

We report here the results of ARISTOTLE-J, a phase II randomized, partially blind, active-controlled study in Japanese patients with non-valvular AF, the primary objective of which was to assess 2 doses of apixaban vs. warfarin for the composite safety endpoint of major and clinically relevant non-major (CRNM) bleeding during a treatment period of 12 weeks. The significance of this study is 2-fold. First, this phase II study was undertaken at the same time that the large, ongoing global phase III ARISTOTLE trial was being conducted. This approach might help to minimize “drug lag” in the evaluation and potential introduction of apixaban into

Japanese clinical practice. Historically, the time elapsed between a drug's approval in Europe or North America and introduction in Japan has been approximately 2.5 years.<sup>31</sup> Second, this is the only phase II study conducted with apixaban in patients with non-valvular AF, and thus it provides initial insights into the potential utility of apixaban vs. warfarin for stroke prevention in this patient population before data from the larger, longer-term phase III ARISTOTLE trial become available.

## Methods

### Patients

This study was conducted at 23 Japanese sites. All subjects gave written informed consent prior to participation. Patients aged  $\geq 20$  years with a history of documented non-valvular AF and at least 1 additional risk factor for stroke were enrolled. Instances of AF (confirmed by electrocardiogram, Holter recording, or intracardiac electrogram) were required to be at least 1 min in duration and to have occurred on 2 separate occasions, at least 2 weeks apart, within 12 months prior to enrollment. Study participants had at least 1 of the following stroke risk factors: age  $\geq 75$  years, congestive heart failure (left ventricular ejection fraction  $\leq 40\%$ ), hypertension requiring medication, diabetes mellitus deemed to require treatment based on the physician's discretion, or history of cerebral infarction or transient ischemic attack (TIA).

Study exclusion criteria included: recent cerebral infarction (including TIA); valvular heart disease; sick sinus syndrome or severe conduction disturbance; non-cardiogenic stroke requiring ASA  $>100$  mg/day or concomitant ASA and antiplatelet agents; contraindications for warfarin use (eg, thrombocytopenic purpura, suspected intracranial bleeding, bleeding tendency due to angiopathy, blood coagulation disorder such as hemophilia, recent major operation, peptic ulcer, or dementia); severe or refractory hypertension; New York Heart Association class IV heart failure; current thrombocytopenia (platelet count  $<100 \times 10^9$ /L or hemoglobin  $<10$  g/dl); liver function test abnormalities (alanine aminotransferase or aspartate aminotransferase  $\geq 2 \times$  upper limit of normal [ULN]) or renal dysfunction (creatinine clearance  $<25$  ml/min by Cockcroft Gault calculation); known or suspected hereditary bleeding tendencies; and scheduled electrical, pharmacological, or surgical cardioversion during the treatment period.

### Study Design

This was a randomized, partially blinded study comparing 2 double-blinded doses of apixaban with open-label warfarin (Figure 1). Subjects were classified as warfarin naïve if they had never received or had received  $\leq 30$  consecutive days of warfarin or another vitamin K antagonist in the past. During a 1-week observation period preceding week 0 (allowable range, 3–14 days), patients who had been receiving warfarin pretreatment had their warfarin dose adjusted or discontinued to achieve an international normalized ratio (INR)  $<2.0$  before entering the 12-week treatment period.

On the first day of study drug dosing (week 0), patients were randomized in a 1:1:1 fashion to receive 12 weeks of double-blinded apixaban 2.5 mg b.i.d., or 5 mg b.i.d., or open-label warfarin titrated to a target INR of 2.0–3.0 in patients aged  $\leq 70$  years and 2.0–2.6 in patients aged  $>70$  years. The randomization assignment method<sup>32</sup> incorporated trial site and warfarin status (experienced or naïve) as factors. Subjects were evaluated at study visits at weeks 1, 2, 4, 8, and 12 (or at study discontinuation if applicable) for bleeding and throm-

boembolic events, other adverse events (AE), and vital signs. Blood samples taken at clinic visits were analyzed by central laboratories for pharmacokinetics, pharmacodynamics (including INR), and clinical laboratory parameters. Follow up was conducted by phone, when possible, 30 days after their last study visit.

The study was conducted according to the Declaration of Helsinki and in compliance with the International Conference on Harmonization and Good Clinical Practice guidelines. All local regulatory requirements and sponsoring company policies were followed. An independent data safety monitoring board advised the study steering committee and study sponsor.

### Study Endpoints

The primary study endpoint was a composite of major bleeding and CRNM bleeding events. Secondary endpoints included major and CRNM bleeding events considered separately, and a composite of total bleeding events (including minor events). The study also included 3 efficacy endpoints: composite of stroke or systemic embolism; composite of stroke, systemic embolism, or all-cause death; and composite of myocardial infarction (MI) or all-cause death. An independent blinded endpoint committee adjudicated all reported bleeding and efficacy events.

Bleeding events were defined using International Society on Thrombosis and Haemostasis (ISTH) criteria.<sup>33</sup> Major bleeds were defined as acute, clinically overt, and with 1 or more of the following: a decrease in hemoglobin  $\geq 2$  g/dl over a 24-h period; bleeding requiring transfusion of  $\geq 2$  units of packed red blood cells; or bleeding in a critical site (intracranial, intraspinal, intraocular [not conjunctival], pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal); or bleeding that was fatal. CRNM bleeding events were defined as acute or subacute, clinically overt, not major, and leading to hospital admission for bleeding, physician-guided medical or surgical treatment for bleeding, or a change in antithrombotic therapy. Minor bleeding was defined as acute clinically overt events not meeting the criteria for either major or CRNM bleeding.

### Pharmacokinetic and Pharmacodynamic Analyses

Blood samples were collected from the apixaban patients at time 0 (pre-dose) and at 1–3 and 3–4 h after dosing in weeks 1 and 8 of treatment, and pharmacokinetic analyses were performed by Alta Analytical Laboratory (El Dorado Hills, CA, USA). Prothrombin time (PT), PT-INR and activated partial thromboplastin time (aPTT) were assessed by SRL Medisearch Inc (USA) and anti-Xa assay was conducted by Esoterix Clinical Trial Services (Engelwood, CO, USA) using a Rotachrom Heparin Assay.

### Statistical Analysis

Target sample size was calculated taking into account the estimated accuracy of the expected difference in the incidence of major and CRNM bleeds between the warfarin (5–8% for the assumption of true incidence) and apixaban (4–9% for the assumption of true incidence) groups. With 70 subjects per treatment group (for a total of 210), the half-length of the 95% confidence intervals (CI) for the difference in proportions of major/CRNM bleeds between each apixaban group and the warfarin group would be 7–9%. In addition, assuming the true incidence of total bleeding would be 16–17% with warfarin and 10–13% with apixaban, 70 subjects per group would give a half-length of the 95%CI for the difference in

Baseline characteristic	Apixaban 2.5 mg b.i.d. (n=74)	Apixaban 5 mg b.i.d. (n=74)	Warfarin (n=74)
Age (mean) (years)	69.3	70.0	71.7
Male, n (%)	63 (85.1)	61 (82.4)	60 (81.1)
Body weight (mean) (kg)	67.6	65.0	64.7
Body mass index (mean) (kg/m <sup>2</sup> )	25.3	24.5	24.4
Blood pressure, systolic/diastolic (mean) (mmHg)	131/77	125/74	126/75
Warfarin experienced*, n (%)	61 (84.7)	62 (87.3)	63 (84.0)
Concomitant ASA use during study*, n (%)	15 (20.8)	20 (28.2)	19 (25.3)
CHADS <sub>2</sub> score** (mean)	1.8	2.1	1.9
0, n (%)	1 (1.4)	1 (1.4)	1 (1.4)
1, n (%)	31 (41.9)	26 (35.1)	36 (48.6)
2, n (%)	25 (33.8)	24 (32.4)	16 (21.6)
≥3, n (%)	17 (23.0)	23 (31.1)	21 (28.4)
Cardiac failure congestive, n (%)	0 (0)	1 (1.4)	2 (2.7)
Hypertension, n (%)	61 (82.4)	61 (82.4)	63 (85.1)
Age ≥75 years, n (%)	22 (29.7)	23 (31.1)	23 (31.1)
Diabetes mellitus, n (%)	21 (28.4)	16 (21.6)	15 (20.3)
History of cerebral infarction (including TIA), n (%)	16 (21.6)	26 (35.1)	20 (27.0)

\*Warfarin experience (%) and concomitant ASA use (%) are based on the safety population (all treated patients).

\*\*CHADS<sub>2</sub>: congestive heart failure, hypertension, age ≥75 years, diabetes (1 point each), stroke (2 points).

ASA, acetylsalicylic acid; TIA, transient ischemic attack.

proportions of all bleeds between each apixaban group and the warfarin group of 11.1–11.8%.

The safety population comprised all randomized patients who received at least 1 dose of the study drug. Efficacy determinations were based on the intent-to-treat population, which included all randomized patients. The proportions of patients with safety and efficacy endpoint events and the corresponding 95%CI were calculated for each treatment group, as were the differences in proportions between each apixaban dose group and the warfarin group. Due to the relatively small number of patients per group, no formal statistical testing was conducted, and therefore P-values were not calculated.

The analyses of bleeding endpoints and all AE included events that occurred during the “treatment period”, defined as starting on the day of first dosing until 2 days after discontinuation of the study drug. Analyses of efficacy endpoints were based on the “intended treatment period”, defined as starting on the day of randomization and ending either 2 days after the last dose of study drug or at the week 12 visit, whichever came last.

## Results

### Patient Disposition and Baseline Characteristics

Of the 245 patients assessed for eligibility, 222 were randomized (74 per treatment group) and were included in the efficacy analysis set (Figure 1). A total of 4 patients discontinued the study without receiving treatment, and 2 randomized to apixaban were treated with warfarin in error and were therefore included in the warfarin treatment group. The remaining 218 patients were included in the safety analysis.

Baseline characteristics were similar across the treatment groups (Table 1). A somewhat lower proportion of patients in the apixaban 2.5 mg b.i.d. group received concomitant aspirin than in the other 2 groups. There were minor differences in the pattern of stroke risk factors: for example, a slightly higher proportion of patients randomized to warfarin had con-

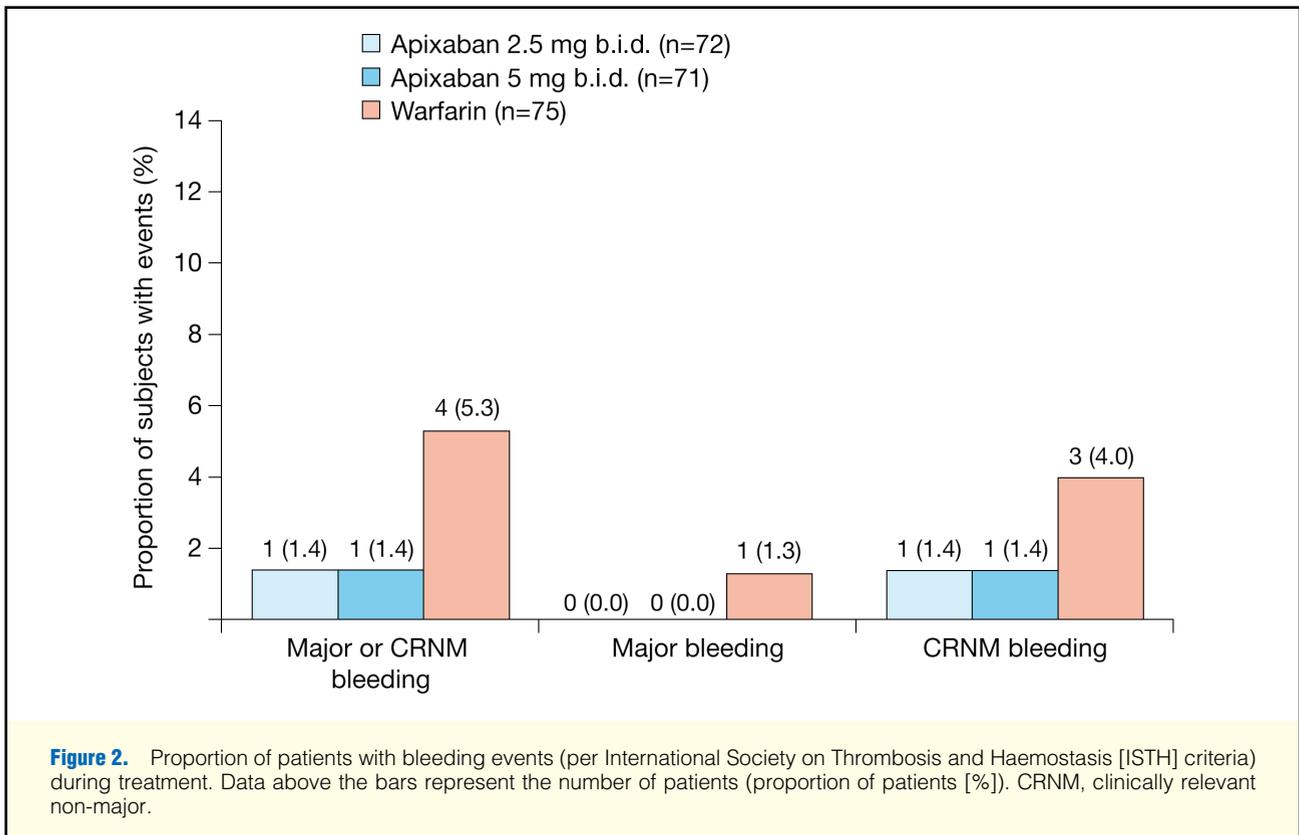
gestive heart failure or hypertension; diabetes mellitus was most common in the apixaban 2.5 mg b.i.d. group; and prior stroke or was most common in the apixaban 5 mg b.i.d. group. Overall, 44.6% of patients had 1 additional risk factor for stroke, 54.1% of patients had 2 or more, and 3 patients (1.4%; 1 in each group) had none. Mean CHADS<sub>2</sub> scores were 1.8, 2.1, and 1.9 in the apixaban 2.5 and 5 mg b.i.d. and warfarin groups, respectively. More than 80% of the patients who received study treatment were classified as warfarin experienced at baseline in each group, and 21–28% received concomitant ASA during the study.

### Treatment Compliance and INR Control

The median duration of treatment was 85 days in each apixaban group and 84 days in the warfarin group. INR was generally well controlled in the warfarin group during the 12-week treatment period: overall ≥60% of patients had INR within the 2.0–3.0 range for 60% of the treatment period according to Rosendaal’s linear interpolation,<sup>34</sup> regardless of whether they were older or younger than 70 years. The proportion was ~70% among patients who were warfarin experienced and ~33% among those who were warfarin naïve. In patients aged ≥70 years, ~70% had INR in the range 1.6–2.6, which is the suggested INR range in the Japanese guidelines for management of stroke for this age group.<sup>8,9</sup>

### Primary Endpoint

The composite of major or CRNM bleeding events occurred in 1 of 72 patients (1.4%; 95%CI, 0.1–6.9) in the apixaban 2.5 mg b.i.d. group, 1 of 71 (1.4%; 95%CI, 0.1–7.0) in the apixaban 5 mg b.i.d. group, and 4 of 75 (5.3%; 95%CI, 1.8–12.7) in the warfarin group (Figure 2). Only one major bleeding event occurred, a subarachnoid hemorrhage in a patient in the warfarin arm. This was in an 80-year-old man who had received therapy with ticlopidine for the past 7 years and warfarin for the past 3 years. The cause of the subarachnoid hemorrhage was unknown and although the INR was gener-



	Apixaban 2.5 mg b.i.d. (n=72)	Apixaban 5 mg b.i.d. (n=71)	Warfarin (n=75)
Epistaxis	3	4*	3
Blood urine present	1	3	3
Gingival bleeding	1	1	0
Hematuria	0	2*	1
Hematochezia	0	2	0
Hemorrhoidal bleeding	1	1	0
Contusion	0	1	1
Retinal hemorrhage	0	0	1
Mouth bleeding	0	0	1
Bite mark	0	1	0
Traumatic hemorrhage	0	1	0
Eczema nummular	1	0	0
Hemorrhage subcutaneous	1	0	0
Subconjunctival hemorrhage	0	1	0
Purpura	0	1	0

\*One patient in the apixaban 5 mg b.i.d. group had an epistaxis and a hematuria event and is counted twice in Table 2.

ally well controlled near the time of the event and during the study the investigator considered the event to be related to warfarin. Regarding CRNM bleeding, the 1 event occurring in the apixaban 2.5 mg b.i.d. arm consisted of epistaxis; for apixaban 5 mg b.i.d. there was 1 case of gastrointestinal hemorrhage; and for warfarin there was 1 epistaxis event, 1 blood in urine event, and 1 conjunctival hemorrhage.

The incidence of minor bleeding was low (Table 2). The

most frequent cause of minor bleeding was epistaxis (3 cases in apixaban 2.5 mg b.i.d., 4 in apixaban 5 mg b.i.d., and 3 in the warfarin group). As indicated in Table 2, although there were numerically more minor bleeding events reported in the apixaban 5 mg b.i.d. group, this was primarily accounted for by single occurrences of various minor bleeding events, such as hemorrhoidal bleeding, contusion, and purpura. Because of these findings for minor bleeding events, the incidence of total bleeding was proportionally highest (23.9%) in the apixaban 5 mg b.i.d. group compared with 12.5% in the apixaban 2.5 mg b.i.d. group and 17.3% with warfarin.

There were no differences in the proportion of patients with total bleeding events when stratified by gender, number of stroke risk factors, history of diabetes mellitus, cerebral infarction, cardiac failure, or hypertension. As expected, older patients had more total bleeding events than younger patients; in the apixaban 2.5 mg b.i.d. arm the proportion of patients with total bleeds was higher among those aged  $\geq 65$  vs.  $< 65$  years (15.1 vs. 5.3%, respectively); in the apixaban 5 mg b.i.d. arm the proportion was higher in those aged  $\geq 75$  vs.  $< 75$  years (38.1 vs. 18.0%, respectively); similarly, in the warfarin arm total bleeds occurred in 32.0% vs. 10.0% in the  $\geq 75$  and  $< 75$  age groups, respectively.

### Stroke, Systemic Embolism, MI, or All-Cause Death

There were no incidences of stroke, systemic embolism, MI, or all-cause death in either apixaban group. In the warfarin group, 3 patients (4.1%) had stroke events: a subarachnoid hemorrhage in 1 patient, considered to be treatment related although INR was well controlled, and ischemic stroke in 2 patients, 1 with INR 2.5 on admission and 1 with INR 2.18. Baseline risk factors for these 3 patients in the warfarin group were age  $\geq 75$  years (2 subjects), history of cerebral infarction

<b>Table 3. Number (%) of Patients With Adverse Events During the Treatment Period</b>			
	<b>Apixaban 2.5 mg b.i.d. (n=72)</b>	<b>Apixaban 5 mg b.i.d. (n=71)</b>	<b>Warfarin (n=75)</b>
<b>Adverse events, n (%)</b>			
All cause	37 (51.4)	42 (59.2)	35 (46.7)
Treatment related*	17 (23.6)	17 (23.9)	10 (13.3)
<b>Serious adverse events, n (%)</b>			
All cause	1 (1.4)	5 (7.0)	4 (5.3)
Treatment related*	0 (0)	0 (0)	1 (1.3)
<b>Discontinuations due to adverse events, n (%)</b>			
All cause	4 (5.6)	4 (5.6)	4 (5.3)
Treatment related*	4 (5.6)	2 (2.8)	1 (1.3)
<b>Deaths due to serious adverse events, n (%)</b>			
All cause	0 (0)	0 (0)	0 (0)
Treatment related*	0 (0)	0 (0)	0 (0)
<b>Most frequent adverse events (&gt;5%) (all cause), n (%)</b>			
Nasopharyngitis	8 (11.1)	8 (11.3)	7 (9.3)
Epistaxis	4 (5.6)	4 (5.6)	4 (5.3)
Blood urine present	1 (1.4)	3 (4.2)	4 (5.3)

\*Includes adverse events whose relationship to the study drug were certain, probable, or possible according to investigators.

tion including TIA (2 subjects), hypertension (2 subjects), and diabetes mellitus (1 subject). One patient (1.4%) in the warfarin group experienced an event that was adjudicated as a TIA. No MI or deaths occurred in the warfarin group.

## AE

The proportion of patients with AE was comparable among the treatment groups, as summarized in **Table 3**, as were proportions with serious AE, discontinuations due to AE, and most frequent all-cause AE. The most frequently reported treatment-related AE were epistaxis (4.2% and 2.8% in the apixaban 2.5 and 5 mg b.i.d. groups, respectively, vs. 5.3% in the warfarin group), and blood in urine (0.0% and 4.2% vs. 4.0%, respectively). Most AE were mild or moderate in severity. Four severe AE (2 in the apixaban 5 mg b.i.d. group and 2 in the warfarin group) were reported. Two were considered treatment related (1 case of trigeminal neuralgia in the apixaban 5 mg b.i.d. group and 1 subarachnoid hemorrhage in the warfarin group). Overall, 12 patients (5.5%) discontinued due to AE (4 in each group).

Occurrence of laboratory abnormalities was similar among all 3 treatment groups. No patients in any of the groups had levels of alanine aminotransferase or aspartate aminotransferase  $>3\times$ ULN. One patient in the apixaban 2.5 mg group had total bilirubin  $>2\times$ ULN at week 8, but it returned to normal in 1 week after discontinuation of concomitant rosuvastatin treatment. Concurrent elevations of aminotransferases  $>3\times$ ULN and total bilirubin  $>1.5\times$ ULN on the same day were not observed in any treatment group. There were no discontinuations that were related to elevation in liver function test results.

## Pharmacokinetics and Pharmacodynamics

Plasma concentrations of apixaban increased over the 3 time points sampled (1, 2, and 4 h after dosing), were proportional to dose, and similar in week 1 and week 8. Anti-Xa activity correlated closely with apixaban concentration, whereas the correlation was weak with PT, PT-INR, and aPTT.

## Discussion

Many important multinational studies have not included patients in Japan, partly because the regulatory system in Japan is different and also due to a perception that cardiovascular event rates are lower and bleeding complications more frequent in Japanese than Western patients.<sup>35</sup> This has contributed, in part, to a “drug lag” wherein the evaluation and approval of new agents are delayed in Japan by approximately 2.5 years compared with other countries.<sup>31</sup> For the ongoing development program evaluating the novel factor Xa inhibitor apixaban for stroke prevention in non-valvular AF, 2 studies have enrolled patients in Japan: ARISTOTLE-J, the phase II study presented here, and ARISTOTLE, the ongoing global phase III trial in  $>18,000$  patients.<sup>29</sup> The approach of conducting ARISTOTLE-J concurrently with the larger, longer-term ARISTOTLE trial might facilitate minimizing “drug lag” in the evaluation and potential availability of apixaban to clinical practice in Japan.

ARISTOTLE-J was a randomized, partially blinded study in which we compared the effect of 2 doses of apixaban (2.5 mg and 5 mg b.i.d.) with adjusted-dose warfarin on the composite of major or CRNM bleeding during a 12-week treatment period in Japanese patients with non-valvular AF and 1 or more additional stroke risk factors. The primary endpoint focused on safety in Japanese patients in this phase II study. Larger phase III studies of longer duration are needed to evaluate efficacy and confirm safety. The number of patients exposed to apixaban in the phase II study will constitute approximately 40% of the overall apixaban safety database in Japanese patients from the phase II and III programs.

Overall, we found only a few cases of the primary endpoint (**Figure 2**): each dose of apixaban was associated with only 1 case of major or CRNM bleeding (1.4%) compared with 4 cases with warfarin (5.3%). No major bleeding events occurred in the apixaban groups, whereas 1 case (1.3%) of subarachnoid hemorrhage occurred in the warfarin group. The incidence of minor bleeding events was also low, accounted for by several cases of epistaxis in each group and single

occurrences of various other events, such as gingival bleeding (Table 2). The low rates of bleeding we observed over the 12 weeks after initiation of anticoagulation therapy are notable given that bleeding rates tend to be higher during that period.<sup>36</sup>

The number of events was too low to determine whether they could have been affected by minor differences in baseline demographics (Table 1); however, we think this is unlikely. Although concomitant aspirin use was lower in the apixaban 2.5 mg b.i.d. group, it was similar in the apixaban 5 mg b.i.d. and warfarin groups. Hypertension, older age, and history of stroke are known to be risk factors for bleeding as well as for stroke.<sup>37</sup> The first 2 of these were present in relatively similar proportions of patients between treatments. A history of stroke was lowest in the apixaban 2.5 mg group but highest in the apixaban 5 mg group. Thus, the rate of events does not seem to consistently correlate with these factors.

Apixaban was well tolerated in this 12-week study. Most AE were either mild or moderate, with few leading to discontinuation. This was also the case in patients treated with open-label warfarin, 80% of whom were warfarin experienced but had undergone a washout period prior to randomization. In addition, we found no elevations of aminotransferases >3× ULN in any of the 3 groups.

Of the agents in development for stroke prevention in AF, phase III results have been published only for dabigatran etexilate, an oral direct thrombin inhibitor. In the RE-LY trial, dabigatran was shown to be superior for stroke prevention, with bleeding rates similar to those with warfarin at a higher dabigatran dose; a lower dose of dabigatran showed similar stroke rates to warfarin, with lower bleeding.<sup>18</sup> In RE-LY, there was a greater rate of dyspepsia (including abdominal pain) in both dabigatran groups compared with warfarin, and a greater rate of treatment discontinuations (~15% vs. 10% at 1 year and 21% vs. 17% at 2 years for dabigatran and warfarin, respectively). MI, although infrequent overall, was more common in the dabigatran groups (0.72% and 0.74%) vs. warfarin (0.53%).<sup>18</sup> In our smaller and shorter duration phase II study, we observed no imbalance in discontinuations and no MI.

In addition to the short duration of the present study, another potential limitation was the use of open-label warfarin. However, the trial design for this phase II study is similar to that used in RE-LY. Furthermore, bleeding and cardiovascular endpoints reported by investigators were centrally adjudicated in a blinded fashion.

In summary, ARISTOTLE-J results show that in Japanese patients with non-valvular AF, oral administration of apixaban 2.5 mg and 5 mg b.i.d. was well tolerated, with lower rates of major/CRNM bleeding than warfarin over 12 weeks. No stroke or systemic embolic events occurred in the apixaban groups. These phase II results add to the emerging clinical trial data on apixaban in patients with non-valvular AF. The phase III AVERROES trial of apixaban compared with aspirin in warfarin-intolerant or warfarin-unsuitable patients was recently stopped early because of a significant benefit in patients randomized to apixaban. Patients randomized to apixaban had a significant reduction in the risk of stroke or systemic embolism compared with patients randomized to aspirin. There was no significant difference between groups in the risk of major bleeding. Thus, results from AVERROES suggest that for AF patients unsuitable for warfarin, apixaban has a favorable risk to benefit profile.<sup>30</sup> For warfarin-tolerant patients, data from our Japanese patient study provide initial insights into the potential clinical utility of apixaban prior to availability

of data from the large, ongoing global phase III ARISTOTLE trial, which also includes patients from Japan.

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### Disclosures

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## Appendix

### ARISTOTLE-J Study Group

Members of the Safety and Efficacy of Apixaban for the Prevention of Stroke in Japanese Subjects with Non-Valvular Atrial Fibrillation (ARISTOTLE-J Study) Study Group are as follows:

**Steering Committee:** Yukito Shinohara (Tachikawa Hospital); Satoshi Ogawa (Mita Hospital).

**Clinical Event Committee:** Masakatsu Nishikawa (Mie University); Hiroyuki Daida (Juntendo University); Makoto Takagi (Tokyo Saiseikai Central Hospital).

**Data and Safety Monitoring Committee:** Hideki Origasa (Toyama University); Mitsuru Murata (Keio University Hospital); Takeshi Yamashita (The Cardiovascular Institute); Masahiro Yasaka (National Kyushu Medical Center).

**Medical Advisory Committee:** Yasuo Ikeda (Waseda University); Shinya Goto (Tokai University).

**Pfizer Japan Clinical Core Team:** Kazuhiro Kanmuri (Japan Clinical Lead); Michinori Terada and Daisuke Shima (Study Clinicians); Hidekazu Murase (Study Manager), Takashi Moriya (Statistician).

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