Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial: Design and rationale

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Atrial fibrillation (AF) is associated with increased risk of stroke that can be attenuated with vitamin K antagonists (VKAs). Vitamin K antagonist use is limited, in part, by the high incidence of complications when patients’ international normalized ratios (INRs) deviate from the target range. The primary objective of ARISTOTLE is to determine if the factor Xa inhibitor, apixaban, is noninferior to warfarin at reducing the combined endpoint of stroke (ischemic or hemorrhagic) and systemic embolism in patients with AF and at least 1 additional risk factor for stroke. We have randomized 18,206 patients from over 1,000 centers in 40 countries. Patients were randomly assigned in a 1:1 ratio to receive apixaban or warfarin using a double-blind, double-dummy design. International normalized ratios are monitored and warfarin (or placebo) is adjusted aiming for a target INR range of 2 to 3 using a blinded, encrypted point-of-care device. Minimum treatment is 12 months, and maximum expected exposure is 4 years. Time to accrual of at least 448 primary efficacy events will determine treatment duration. The key secondary objectives are to determine if apixaban is superior to warfarin for the combined endpoint of stroke (ischemic or hemorrhagic) and systemic embolism, and for all-cause death. These will be tested after the primary objective using a closed test procedure. The noninferiority boundary is 1.38; apixaban will be declared noninferior if the 95% CI excludes the possibility that the primary outcome rate with apixaban is \( \geq 1.38 \) times higher than with warfarin. ARISTOTLE will determine whether apixaban is noninferior or superior to warfarin in preventing stroke and systemic embolism; whether apixaban has particular benefits in the warfarin-naïve population; whether it reduces the combined rate of stroke, systemic embolism, and death; and whether it impacts bleeding. (Am Heart J 2010;159:331-9.)

Atrial fibrillation (AF) is a growing public health problem worldwide and is the most common arrhythmia requiring hospitalization in the United States. The incidence of AF has increased over the past 2 to 3 decades. The number of people with AF in the United States is projected to exceed 10 million by 2050; this will be accompanied by substantial morbidity and mortality. Stroke is considered to be the most significant morbidity in patients with AF. Approximately 15% of strokes occur in those with AF and the risk of stroke in untreated AF patients averages 5% per year. The annual risk of stroke in AF patients is related to age, increasing from 1.5% for patients aged 50 to 59 years to 23% for those aged 80 to 89 years. When compared with stroke from other causes, ischemic stroke secondary to AF carries twice the risk of death.

Warfarin

Warfarin, a vitamin K antagonist (VKA), reduces the risk of stroke by approximately 62%; however, VKAs have major limitations and are underused in clinical practice. Patients are frequently outside the optimal target anticoagulation range when VKAs are prescribed, exposing them to the risk of thrombosis or bleeding. Clinical trial data show that among patients receiving
warfarin or other VKAs, even in the highly structured setting of a trial, the international normalized ratio (INR) is outside the therapeutic range (2.0-3.0) about one third of the time.\textsuperscript{10-13} Moreover, a meta-analysis shows that the proportion of time outside the therapeutic INR range in community practice is 43\%.\textsuperscript{11} Thus, a large number of patients with AF who should be on warfarin are either not deriving full benefit from warfarin or are not receiving it at all. Not only do VKAs have a narrow therapeutic window but they also exhibit a highly variable dose response that is attributable to genetic, disease-related, and environmental factors. Their dosing can be particularly challenging among elderly individuals due to changes in the pharmacokinetics and pharmacodynamics that occur with age. Other factors influencing drug effect include prescription and nonprescription drugs, dietary vitamin K, and botanical products.\textsuperscript{14,15} The need for regular and lifelong therapeutic monitoring is an inconvenience for many patients. These limitations of VKAs illustrate the need for new oral anticoagulants for the prevention of thromboembolism in patients with AF.

Current guidelines, including those from the American College of Cardiology/American Heart Association/European Society of Cardiology, recommend a risk-based approach for antithrombotic therapy for stroke prevention.\textsuperscript{16} Aspirin or VKAs are recommended for patients with AF who have one moderate risk factor for stroke (CHADS\(_2\) risk score of 1), and VKAs are recommended for patients with more than one moderate risk factor (CHADS\(_2\) risk score \(\geq\)2) for stroke.\textsuperscript{16} Vitamin K antagonists are efficacious at preventing stroke even in the lower risk AF population\textsuperscript{17}; however, their routine use is not currently recommended because the overall net benefit in this low-risk group is uncertain. Because the oral factor Xa inhibitors avoid many of the limitations of VKAs, it is important to evaluate these new agents across the spectrum of risk including patients with a low to intermediate risk of stroke.

Another important issue is that in patients starting warfarin for the first time, the risk of thromboembolism and bleeding is high for the first year due in part to the time taken to establish an adequate and stable INR. In one observational study, patients starting warfarin had a 3-fold increased risk of bleeding in the first 90 days of treatment\textsuperscript{7} compared with patients already on warfarin.\textsuperscript{7} The ACTIVE-W study showed that, in patients with AF at high risk of stroke, warfarin was superior to clopidogrel plus aspirin for prevention of vascular events.\textsuperscript{18} Additional analyses also showed that the rates of discontinuation of warfarin therapy during the first year of the trial were higher (15\%) in the warfarin-naïve patients when compared with the warfarin-experienced patients (8\%).\textsuperscript{19}

In antithrombotic therapy for the prevention of thromboembolism in patients with AF, there is a need for an alternative to warfarin that has greater efficacy, greater convenience of use, and/or greater safety. When compared with warfarin in the SPORTIF III and V trials, the oral direct thrombin inhibitor ximelagatran was found to be effective with an acceptable bleeding risk,\textsuperscript{10,12} but its development was stopped due to liver toxicity. A number of new anticoagulants, including factor Xa inhibitors and direct thrombin inhibitors, are now being developed and evaluated as alternatives to warfarin for stroke prevention in AF. The ideal agent should be oral and free from variation in absorption related to food intake and should have predictable pharmacokinetics, few drug interactions, and minimal toxicity. It would not require therapeutic monitoring and its efficacy and safety would be comparable with or superior to warfarin at preventing thromboembolism in AF subjects.

**Apixaban**

Factor Xa occupies a pivotal role in the clotting cascade because it promotes conversion of prothrombin to thrombin. Developed as an anticoagulant agent, apixaban is an orally active selective inhibitor of the coagulation factor Xa. The direct mechanism of this drug does not require the presence of antithrombin. It has a predominantly nonrenal (75\%) clearance and a half-life around 12 hours in healthy volunteers. The effect is independent of vitamin K intake, and with the exception of strong CYP3A4 inhibitors, there is minimal potential for drug-to-drug interaction. This compound has shown efficacy in preclinical animal models for venous and arterial thrombosis and has no organ-specific toxicity in animal models of up to 12 months of exposure.\textsuperscript{20,21}

In a phase II dose-ranging study of deep vein thrombosis (DVT) prevention in patients undergoing knee replacement surgery, pooling of all doses of apixaban showed a 21\% reduction in venous thromboembolism (VTE) or all-cause death when compared with enoxaparin and a 53\% reduction in VTE or all-cause death when compared with warfarin.\textsuperscript{22} Importantly, the frequency of major bleeding events was low (0\%-3.3\%) and comparable among all apixaban arms. A dose-ranging trial in DVT treatment including 520 patients with proximal DVT also showed favorable efficacy and safety, including the 5 mg twice a day apixaban dose arm.\textsuperscript{23}

The ADVANCE-1 study, a phase III VTE prevention trial, compared apixaban, 2.5 mg, twice daily with the Food and Drug Administration-approved dose of enoxaparin (30 mg twice daily).\textsuperscript{24} The primary efficacy outcome was a composite of symptomatic or asymptomatic DVT, pulmonary embolism, and death from any cause. In a preliminary analysis, the rate of the primary efficacy endpoint in the apixaban arm was similar to that observed with enoxaparin (9.0\% vs 8.9\%, \(P = .64\)). The major bleeding rate for apixaban, however, tended to be
lower than for enoxaparin (0.7% vs 1.4%, \( P = .053 \)), and the composite rate of clinically relevant nonmajor bleeding and major bleeding was significantly lower in patients assigned to apixaban than those assigned to enoxaparin (2.9% vs 4.3%, \( P = .034 \)).

APPRaise was a phase II, randomized, double-blind, placebo-controlled, parallel arm study that enrolled 1,715 patients with acute coronary syndrome (ACS) from Europe and North America.\(^{25}\) This study demonstrated that the addition of apixaban to current antplatelet therapy for 6 months after ST elevation or non-ST elevation ACS results in a dose-dependent increase in bleeding and a trend toward a reduction in ischemic events. Based on these data, apixaban at a total daily dose of between 5 and 10 mg is being tested in patients with ACS receiving aspirin or dual antplatelet therapy in the phase III trial APPRAISE 2.

These findings indicate that oral factor Xa inhibition at a dose of 5 to 10 mg daily may be an effective and safe approach toward anticoagulation. Based on the experience in DVT prevention and treatment trials, a dose of 5 mg twice a day of apixaban was chosen for comparison with warfarin for prevention of stroke and systemic embolism in patients with AF in the ARISTOTLE trial.

### Study objectives

#### Primary objective

The primary objective of this study is to determine whether apixaban is noninferior to warfarin (INR target range 2.0-3.0) at reducing the combined outcome of stroke (ischemic or hemorrhagic) and systemic embolism in subjects with AF and at least 1 additional risk factor for stroke.

#### Secondary objectives

The key secondary objectives are to determine if apixaban is superior to warfarin for the combined endpoint of stroke (ischemic or hemorrhagic) and systemic embolism, and for all-cause death. These will be tested after the primary objective using a closed test procedure.

Other secondary objectives are to compare apixaban and warfarin with respect to:

- The composite endpoint of ischemic stroke, hemorrhagic stroke, systemic embolism, and all-cause death,
- The composite endpoint (in warfarin-naïve patients) of ischemic stroke, hemorrhagic stroke, systemic embolism and major bleeding,
- The composite endpoint of ischemic stroke, hemorrhagic stroke, systemic embolism, and major bleeding,
- The composite endpoint of ischemic stroke, hemorrhagic stroke, systemic embolism, major bleeding, and all-cause death,
- The composite endpoint of ischemic stroke, hemorrhagic stroke, systemic embolism, myocardial infarction, and all-cause death,
- Major bleeding

### Study population

In this double-blind study, we have randomized 18,206 patients with AF from over 1,000 centers in about 40 countries. Eligible subjects were randomly assigned in a 1:1 ratio to receive either apixaban or warfarin titrated to a target INR range of 2.0 to 3.0. Both warfarin-naïve and warfarin-experienced patients are being recruited, with a

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**Table I. Inclusion and exclusion criteria**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tr>
<td>Age ( \geq 18 ) y</td>
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<tr>
<td>Permanent or persistent AF or atrial flutter on ECG at enrollment; or AF or atrial flutter documented by ECG or as an episode ( \geq 1 ) min on rhythm strip, Holter monitor, or intracardiac recording on 2 separate occasions at least 2 wk apart in 12 mo before enrollment</td>
</tr>
</tbody>
</table>

One or more of the following risk factors for stroke

- Age \( \geq 75 \) y
- Prior stroke, TIA, or systemic embolus
- Symptomatic CHF within 3 mo or LV dysfunction with LVEF \( \leq 40\% \) by echocardiography, radionuclide study, or contrast angiography
- Diabetes mellitus
- Hypertension requiring pharmacologic treatment
- Women of childbearing potential must use contraception to avoid pregnancy during treatment period or for 2 wk after last dose of study medication, whichever is longer
- All subjects must provide signed written informed consent

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>AF or atrial flutter due to reversible causes (eg, thyrotoxicosis, pericarditis)</td>
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<tr>
<td>Clinically significant (moderate or severe) mitral stenosis</td>
</tr>
<tr>
<td>Increased bleeding risk believed to be a contraindication to oral anticoagulation (eg, previous intracranial hemorrhage)</td>
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<tr>
<td>Conditions other than AF that require chronic anticoagulation (eg, prosthetic mechanical heart valve)</td>
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<tr>
<td>Persistent uncontrolled hypertension (SBP &gt; 180 mm Hg or DBP &gt; 100 mm Hg)</td>
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<tr>
<td>Active infective endocarditis</td>
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<tr>
<td>Planned major surgery</td>
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<tr>
<td>Planned AF or atrial flutter ablation procedure</td>
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<tr>
<td>Use of unapproved investigational drug or device in past 30 d</td>
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<tr>
<td>Required aspirin &gt; 165 mg/d</td>
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<tr>
<td>Simultaneous treatment with both aspirin and a thienopyridine (eg, clopidogrel, ticlopidine)</td>
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<tr>
<td>Severe comorbid condition with life expectancy ( \leq 1 ) y</td>
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<tr>
<td>Active alcohol or drug abuse or psychosocial reasons that make study participation impractical</td>
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<tr>
<td>Recent stroke (within 7 d)</td>
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<tr>
<td>Severe renal insufficiency (serum creatinine level &gt; 2.5 mg/dl or calculated creatinine clearance &lt; 25 mL/min)</td>
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<tr>
<td>ALT or AST &gt; 2 × ULN or a total bilirubin &gt; 1.5 × ULN (unless an alternative causative factor [eg, Gilbert’s syndrome] is identified)</td>
</tr>
<tr>
<td>Platelet count &lt; 100,000/mm(^3)</td>
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<tr>
<td>Hemoglobin level &lt; 9 g/dl</td>
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<td>Inability to comply with INR monitoring</td>
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ECG, Electrocardiogram; CHF, congestive heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine transaminase; AST, aspartate transaminase; ULN, upper limit of normal; wk, weeks; mo, months.
special emphasis on the former. Our aim is for 40% of patients to be warfarin naïve. The inclusion and exclusion criteria are summarized in Table I.

**Randomization and study drug**

Subjects who were on warfarin before randomization discontinued the drug 72 hours before randomization and were not dosed with study drug until the INR was <2.0. Randomization is stratified by investigative site and prior warfarin use status (experienced or naïve). Patients are classified as warfarin naïve if they have never used warfarin (or other VKAs) or if they have used it for ≤30 consecutive days. Otherwise, patients are considered warfarin experienced.

To maintain blinding, study medications are packaged using a double-dummy design. The 2 sets of tablets each subject receives are distinguishable by color and size, but active apixaban tablets match placebo apixaban tablets and active warfarin tablets match placebo warfarin tablets to ensure blinding of the patient and investigator. After randomization, patients receive either apixaban and warfarin placebo or apixaban placebo and warfarin. During the titration phase, we recommend the use of a dosing algorithm with initial daily dose of up to 6 mg of warfarin (or warfarin placebo) (unless already on a stable dose of warfarin, in which case that may be continued) and dose of apixaban (or apixaban placebo) of 5 mg twice a day. For patients who are estimated to have higher apixaban drug exposure, we will use a lower dose of 2.5 mg twice a day of apixaban. Subjects who fulfill any 2 of the following criteria at baseline will receive the lower apixaban dose of 2.5 mg twice a day: age ≥80 years, body weight ≤60 kg, and serum creatinine level ≥1.5 mg/dL (133 μmol/L). Subsequent warfarin doses are recommended based upon an algorithm provided to the investigators; however, the final dose decision is left to the discretion of the investigator. Subjects, investigators, members of the steering and adjudication committees, and the sponsor's staff conducting the study do not have access to individual subject treatment assignments.

**Study design and duration**

The trial is event driven, thus, the number of subjects required and length of treatment were estimated based on event rates in similar trials. The final duration of the trial will be determined by the time required to accrue at least 448 primary efficacy events (see statistical methods). All subjects will be followed from randomization until the study end date.

The study includes a screening period of up to 14 days. Subjects with AF and at least ≥1 risk factors for stroke will be evaluated for study eligibility. The design of the study is shown in Figure 1.

**INR monitoring**

The INR monitoring for the warfarin-naïve patients begins on the fourth day after initiation of study drug and is performed twice a week for 2 weeks, once a week for 2 weeks, and monthly thereafter once a stable INR is attained. For the warfarin-experienced patients who have been on stable dosing of VKA for at least 3 months, INR monitoring visits are required on day 1, week 1, week 2, and then monthly. An investigator may increase the frequency of INR monitoring if it is considered clinically indicated.

Titration of the study drug is based on central monitoring of INR measurements using encrypted point-of-care (POC) devices, centralized dosing recommendations, and sham apixaban titration. The POC device delivers an encrypted result to the investigator who telephones or electronically transmits the result along with the subject's identification number, date, and time to a central response system. This system processes the information in a blinded manner and returns either a true INR value (if a subject is receiving warfarin) or a sham INR value (if a subject is receiving apixaban). Although investigators will need to obtain open label INR values when clinically indicated, efforts will be made to minimize nonstudy INR assessments. The final dosing decision rests with the investigator. Assessments of outcomes and study medication compliance are performed at each INR visit.

**Follow-up**

The follow-up period will last until the attainment of at least 448 primary study events. Follow-up of subjects who discontinue study drug will occur quarterly until the end of the study.

**Outcome definitions**

**Efficacy outcomes**

The primary efficacy outcome is the time to first occurrence of stroke (ischemic or hemorrhagic) or systemic embolism.

In this study, stroke is defined as a nontraumatic abrupt onset of a focal neurologic deficit lasting at least 24 hours. A retinal ischemic event (embolism or thrombosis) will be considered a stroke. A cerebral imaging study (computed tomographic scan or magnetic resonance imaging) is recommended for all suspected strokes. Strokes will be classified as ischemic, ischemic with hemorrhagic transformation, hemorrhagic, or of uncertain type. Hemorrhagic strokes will be subclassified as subdural, subarachnoid, or intraparenchymal.

A transient ischemic attack (TIA) is defined as a nontraumatic abrupt onset of a focal neurologic deficit lasting <24 hours. Stroke and TIA will be further subclassified based on whether there is imaging evidence of a new cerebral infarction that correlates with the clinical presentation of the subject.
The diagnosis of systemic embolism requires a clinical history consistent with an acute loss of blood flow to a peripheral artery (or arteries) supported by evidence of embolism from surgical specimens, autopsy, angiography, vascular imaging, or other objective testing.

Safety outcomes

The primary safety endpoint is time to first occurrence of confirmed major bleeding.

The definition of major bleeding described below is adapted from the protocol and the International Society on Thrombosis and Hemostasis definition. The baseline hemoglobin level is defined as the closest hemoglobin level value before the bleeding event.

Major bleeding is defined as acute or subacute clinically overt bleeding accompanied by ≥1 of the following: (1) a decrease in hemoglobin level of ≥2 g/dL over a 24-hour period; (2) a transfusion of ≥2 U of packed red blood cells; and/or (3) bleeding that is fatal or occurs in at least 1 of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, retroperitoneal.

Clinically relevant nonmajor bleeding is defined as acute or subacute clinically overt bleeding that does not satisfy the criteria for major bleeding and leads to hospital admission for bleeding, physician-guided medical or surgical treatment for bleeding, or a change in antithrombotic therapy (including study drug) for bleeding.

All acute clinically overt bleeding events not meeting the criteria for either major bleeding or clinically relevant nonmajor bleeding are classified as minor bleeding.

Bleeding events are also classified by the TIMI and GUSTO criteria.27

The secondary safety outcome for this trial is a composite of major bleeding and clinically relevant nonmajor bleeding. Other safety outcome measures include minor bleeding, fractures, and other adverse events.

Clinical Events Committee adjudication

An independent, blinded, clinical events committee (CEC) adjudicates all suspected hemorrhagic and nonhemorrhagic strokes, TIsAs, systemic emboli, major and clinically relevant non-major bleeding, myocardial infarction, and cause of death.

Using prespecified event definitions and agreed upon event adjudication criteria, the CEC adjudicates suspected events based on the preponderance of the evidence and the clinical knowledge and experience of the physician reviewers. Event adjudication in ARISTOTLE occurs in 2 phases. All suspected events are adjudicated in phase I. Each stroke, systemic embolism, and bleeding event are reviewed by 2 independent physician reviewers. Each myocardial infarction and death event are reviewed by 1 reviewer. Significant disagreements between phase I reviewers for stroke, systemic embolism, and bleeding cases are identified as needing phase II review. In addition, a quality control sample undergoes phase II review. All phase II reviews are conducted by committee with the final adjudicated result being a consensus of the committee members present. In both phase I and phase II reviews, all stroke events are evaluated by at least 1 neurologist.
Statistical analysis and sample size calculation

A meta-analysis of 6 AF studies estimated a relative reduction in the risk of stroke or systemic thromboembolism of 62% for warfarin versus placebo. Based on historical trials, the primary noninferiority hypothesis of ARISTOTLE is that apixaban will preserve at least 50% of the benefit of warfarin in preventing stroke and systemic embolism. This gives an upper CI of 1.88 of the apixaban versus warfarin relative risk (Figure 2A). To be more certain that apixaban is noninferior to warfarin based on this single clinical trial, more stringent boundaries are defined. In response to different international regulatory bodies, 2 noninferiority tests will be applied. First, the 95% CI should not include ≥1.38 to declare noninferiority (Figure 2B). In addition, the 99% CI should not include ≥1.44 to declare noninferiority. Because the event rate is lower than initially expected, it is estimated that approximately 18,000 randomized patients with sufficient risk of stroke and sufficient treatment duration will result in 448 patients with primary outcome events needed for 90% power to meet the primary objective of the study. We originally estimated that the follow-up would be an average of 1.8 years, assuming a stroke or systemic embolism rate of 1.67 per 100 subject-years.

An independent Data Monitoring Committee is charged with monitoring the accumulating trial data. A formal interim analysis will be performed once 50% of the primary efficacy endpoint events have been confirmed by the CEC. The objective of this interim analysis is to determine whether apixaban is superior to warfarin for the primary efficacy endpoint. No interim testing for noninferiority will be performed.

Pharmacokinetic biomarkers

The main objectives of the biomarker and genetic substudy program are to correlate genetic polymorphisms and levels of biomarkers with clinical outcomes, to improve risk stratification for stroke among patients with AF, and to relate the effects of apixaban and warfarin to these disease biomarkers. Several biomarkers will be analyzed at baseline for as many of the 18,206 patients as possible (Table II), and a second blood sample will be collected for approximately 5,000 patients at 2 months. This will allow the analysis of changes in biomarker levels.

Organizational structure

The ARISTOTLE trial is led by an academic steering committee composed of 2 cochairs, national coordinators from each participating country, and a representative from the trial sponsor. This committee provides scientific direction and input, addresses policy issues regarding the protocol, and meets periodically to assess the trial progress.

The ARISTOTLE executive committee, composed of a subset of senior leaders from the steering committee, is responsible for evaluating the progress and safety of the trial and making decisions regarding early termination or continuation of the trial.

A subset of the steering committee will form the publications committee that will oversee the publication
process for the main manuscript and all secondary presentations and manuscripts resulting from the trial.

The ARISTOTLE Trial is sponsored and funded by Bristol-Myers Squibb (Princeton, NJ, USA) and Pfizer (New York, NY, USA).

Discussion

Atrial fibrillation is a very common arrhythmia and is associated with an increased risk of mortality and morbidity, particularly stroke, which is the third most common cause of death in developed countries and the leading cause of serious long-term disability worldwide.28

The ACTIVE-W study included 6,706 patients with AF and at least ≥1 risk factors for stroke.18 ACTIVE-W was designed to compare oral anticoagulation therapy with aspirin plus clopidogrel for prevention of vascular events in patients with AF at high risk for stroke. This study was not blinded. Moreover, there was no requirement for a certain proportion of warfarin-naïve patients. At study entry, approximately 76% of the patients were on warfarin. The study was stopped early because of the superiority of warfarin over aspirin plus clopidogrel for prevention of vascular events in patients with AF. These results were driven by the higher rates of stroke on clopidogrel plus aspirin.

Several oral direct thrombin inhibitors are being tested for stroke prevention in patients with AF such as ximelagatran and dabigatran.29 This class of drug has a wider therapeutic range than warfarin, low potential for food and drug interactions, and no requirements for dose adjustments or regular monitoring. The SPORTIF III and V trials involving 3,407 and 3,922 patients, respectively, showed no difference in stroke prevention between ximelagatran and warfarin.10,12 However, there was a significant increase in the level of liver enzymes in patients on ximelagatran. Moreover, major adverse cardiovascular events were observed in other studies,30,31 and the drug was withdrawn from all markets in 2006. In addition, there was an unexplained higher rate of major bleeding in SPORTIF V when compared with SPORTIF III. Recently the RE-LY open label trial reported the results comparing 110 mg twice daily and 150 mg twice daily of the oral thrombin inhibitor dabigatran versus warfarin in 18,113 AF patients with at least one risk factor for stroke.35 In this study dabigatran 150 mg twice daily was superior and 110 mg twice daily noninferior concerning stroke while simultaneously both doses reduced intracranial and life-threatening hemorrhage.32 Therefore, there is now a larger focus on testing for potential superiority of apixaban over warfarin in the current trial.

Other phase III trials are testing inhibitors of factor Xa for stroke prevention in patients with AF. ROCKET-AF is comparing warfarin with rivaroxaban in a double-blind trial of 14,000 patients with AF at high risk for stroke.35 AVERROES is another double-blind trial of apixaban in comparison with aspirin in 5,600 patients with AF and moderate risk of stroke or intolerance to warfarin.34 BOREALIS-AF is testing subcutaneous weekly injections of biotinylated idraparinux, a subcutaneous indirect factor Xa inhibitor, in patients with AF and high risk of stroke.35 This trial is designed as a double-blind comparison of idraparinux with warfarin in 9,600 patients.

ARISTOTLE will define whether apixaban is noninferior or/and superior to warfarin in the overall population and whether it may be superior solely in the warfarin-naïve population, which is more susceptible to complications until a stable warfarin dose has been established and more prone to warfarin discontinuation.

Important features of the ARISTOTLE trial include the investigation of a drug with a relatively long half-life and robust phase II to III data on safety and efficacy of the tested dose for DVT prophylaxis, the double-blind design with use of encrypted POC INR monitoring devices, good representation of warfarin-naïve patients, inclusion of the full risk-spectrum of patients (CHADS2 score ≥1),

### Table II. Biomarkers

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Area</th>
<th>Characteristic</th>
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<tbody>
<tr>
<td>hs-Troponin I</td>
<td>Myocardial necrosis, myocardial function</td>
<td>Strong predictor for raised mortality in ACS and in healthy elderly</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>Myocardial necrosis, myocardial function</td>
<td>↑ in patients with AF; high levels indicate increased risk for thromboembolism</td>
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<tr>
<td>ADMA</td>
<td>Endothelial function</td>
<td>↑ in patients with vascular disease</td>
</tr>
<tr>
<td>vWF</td>
<td>Endothelial function</td>
<td>↑ levels in AF patients; predictor for vascular events</td>
</tr>
<tr>
<td>hs-CRP, IL-6</td>
<td>Inflammation</td>
<td>Associated with AF and risk of future CV events in healthy individuals</td>
</tr>
<tr>
<td>Soluble CD40 ligand</td>
<td>Platelet activity</td>
<td>↑ levels related to inflammatory activity, coagulation, and platelet activation</td>
</tr>
<tr>
<td>Fragment 1+2</td>
<td>Coagulation</td>
<td>↑ in patients with AF and related to risk factors for stroke; reduced with warfarin treatment</td>
</tr>
<tr>
<td>D-dimer</td>
<td>Coagulation</td>
<td>↑ in patients with AF and associated with new thrombotic events; reduced with warfarin treatment</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>Renal function</td>
<td>↑ in patients with reduced renal function; poorer prognosis in patients with CV disease; better marker for endogenous GFR than creatinine clearance</td>
</tr>
<tr>
<td>HbA1c, Apo A, Apo B</td>
<td>Metabolism and lipoproteins</td>
<td>Lipoproteins and diabetes mellitus risk factors for CV disease; diabetes mellitus predictor of an increased risk for complications</td>
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BNP, Brain natriuretic peptide; CV, cardiovascular; GFR, glomerular filtration rate.
multinational representation of various health care systems and ethnic groups, and modification of dose of the study drug for patients with the highest drug exposure (2 criteria of older age, renal insufficiency, or low body weight). In ARISTOTLE, the protocol provides guidance on management of bleeding. Most bleeding can be managed by discontinuation of antithrombotic therapy (including study medication), local hemostatic measures, and fresh frozen plasma as needed. Patients with ongoing serious or life-threatening bleeding may require unblinding to guide reversal with vitamin K, and consideration of use of prothrombin complex concentrate, if on warfarin. For patients on apixaban, reversal of the anticoagulant effects will occur relatively rapidly over time given its halflife of around 12 hours. Apixaban has no specific antidote or reversal agent. Other agents, such as recombinant activated factor VII (NovoSeven, Novo Nordisk A/S, Bagsvaerd, Denmark), have not been studied in this setting and are not recommended.

Conclusion
In conclusion, the ARISTOTLE trial will answer many important questions related to stroke prevention in AF. Most importantly, it will compare apixaban with warfarin for stroke prevention in a wide range of patients with AF. It will provide information about the efficacy of apixaban both in warfarin-experienced and warfarin-naive patients. Finally, it will generate a better understanding of this common disease and the risks of stroke and bleeding based on large scale substudies on genetic and protein biomarkers.

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