Apixaban in Comparison With Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease

Findings From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial

Alvaro Avezum, MD, PhD; Renato D. Lopes, MD, PhD, MHS; Phillip J. Schulte, PhD; Fernando Lanas, MD; Bernard J. Gersh, MB, ChB, DPhil; Michael Hanna, MD; Prem Pais, MD; Cetin Erol, MD; Rafael Diaz, MD; M. Cecilia Bahit, MD; Jozef Bartunek, MD, PhD; Raffaele De Caterina, MD, PhD; Shinya Goto, MD, PhD; Witold Ruzyllo, MD, PhD; Jun Zhu, MD; Christopher B. Granger, MD; John H. Alexander, MD, MHS

Background—Apixaban is approved for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. However, the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial included a substantial number of patients with valvular heart disease and only excluded patients with clinically significant mitral stenosis or mechanical prosthetic heart valves.

Methods and Results—We compared the effect of apixaban and warfarin on rates of stroke or systemic embolism, major bleeding, and death in patients with and without moderate or severe valvular heart disease using Cox proportional hazards modeling. Of the 18,201 patients enrolled in ARISTOTLE, 4,808 (26.4%) had a history of moderate or severe valvular heart disease or previous valve surgery. Patients with valvular heart disease had higher rates of stroke or systemic embolism and bleeding than patients without valvular heart disease. There was no evidence of a differential effect of apixaban over warfarin in patients with and without valvular heart disease in reducing stroke and systemic embolism (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.51–0.97 and HR, 0.84; 95% CI, 0.67–1.04; interaction P=0.38), causing less major bleeding (HR, 0.79; 95% CI, 0.61–1.04 and HR, 0.65; 95% CI, 0.55–0.77; interaction P=0.23), and reducing mortality (HR, 1.01; 95% CI, 0.84–1.22 and HR, 0.84; 95% CI, 0.73–0.96; interaction P=0.10).

Conclusions—More than a quarter of the patients in ARISTOTLE with nonvalvular atrial fibrillation had moderate or severe valvular heart disease. There was no evidence of a differential effect of apixaban over warfarin in reducing stroke or systemic embolism, causing less bleeding, and reducing death in patients with and without valvular heart disease.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00412984.

(Circulation. 2015;132:624-632. DOI: 10.1161/CIRCULATIONAHA.114.014807.)

Key Words: apixaban ■ atrial fibrillation ■ heart diseases ■ hemorrhage ■ oral anticoagulant ■ stroke ■ valvular heart disease

Valvular heart disease is common worldwide although the etiology varies by region. In higher-income countries, the most common cause of valvular heart disease is degenerative, whereas in developing regions, rheumatic heart disease is the main cause.1–4 Valvular heart disease, independent of the underlying cardiac rhythm, is associated with a higher risk of thromboembolic events.5 Atrial fibrillation is associated with a substantially higher risk of thromboembolism in patients with rheumatic mitral stenosis.6 Oral anticoagulation with vitamin K antagonists is indicated for the prevention of stroke and systemic embolism in patients with cardiac valve replacement and in patients with atrial fibrillation and mitral stenosis.7,8 The term valvular atrial fibrillation arose at the time of the original warfarin trials9 to describe patients with rheumatic mitral stenosis or prosthetic heart valves, who were deemed at such high risk of stroke without warfarin that it would be unethical to assign them to control10 (Jonathan L. Halperin, MD, personal communication, June 2014). In the Apixaban for Reduction in
Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, apixaban, a direct oral factor Xa inhibitor, was found to reduce stroke or systemic embolism, cause less bleeding, and reduce mortality in comparison with warfarin and has been approved for stroke prevention in nonvalvular atrial fibrillation. The ARISTOTLE trial excluded patients with moderate or severe mitral stenosis and mechanical prosthetic heart valves, but included a substantial number of patients with other valvular heart disease, thus offering an opportunity to evaluate the effect of apixaban in comparison with warfarin in patients with atrial fibrillation and valvular heart disease.11

Methods

Patient Population
The design and results of the ARISTOTLE trial have been published (clinicaltrials.gov NCT00412984).12 In brief, ARISTOTLE was a noninferiority trial to compare apixaban with warfarin in patients with atrial fibrillation and at least 1 additional risk factor for stroke. Exclusion criteria included clinically significant (moderate or severe) mitral stenosis, indications for oral anticoagulation other than atrial fibrillation (including mechanical prosthetic heart valves), and planned use of concomitant high-dose aspirin (>165 mg/d) or dual-antiplatelet therapy. Patients with valvular heart disease, including aortic stenosis, aortic regurgitation, mild mitral stenosis, mitral regurgitation, tricuspid stenosis, tricuspid regurgitation, valve repair, or bioprosthesis valve replacement were eligible for enrollment in ARISTOTLE. Patients were considered to have valvular heart disease if they had (1) a history of at least moderate valvular heart disease, (2) baseline echocardiographic evidence of at least moderate valvular heart disease, or (3) a history of previous valve surgery reported on the trial case report form. All data regarding valvular heart disease were site reported based on available medical history. There was no central echocardiography laboratory confirming valvular heart disease or its severity. All patients provided written informed consent, and approval by the appropriate institutional review boards/ethics committees was obtained at all sites.

Patients were randomly assigned to apixaban 5.0 mg twice daily and warfarin placebo or to dose-adjusted warfarin (target international normalized ratio of 2.0–3.0) and apixaban placebo. A 2.5-mg dose of apixaban was used in patients randomly assigned to apixaban with ≥2 of the following: age ≥80 years, body weight ≥60 kg, or serum creatinine ≥133 μmol/L (1.5 mg/dL).

Objectives
The objectives of this secondary analysis were to (1) describe the frequency and characteristics of valvular heart disease in the ARISTOTLE population; (2) compare the rates of stroke or systemic embolism, major bleeding, and death in patients with atrial fibrillation with and without valvular heart disease; and (3) assess the efficacy and safety of apixaban in comparison with warfarin in patients with atrial fibrillation with and without valvular heart disease.

Clinical Outcomes
The primary outcome was stroke or systemic embolism, and the main safety outcome was major bleeding as defined by the International Society on Thrombosis and Haemostasis.13,14 The key secondary efficacy outcome was death from any cause. All efficacy and safety outcome events were adjudicated by a blinded clinical events committee with the use of prespecified criteria.

Statistical Methods
Baseline characteristics, risk factors, and concomitant medications are described by valvular heart disease status and randomized treatment. Continuous variables are presented as the median with 25th and 75th percentiles, and categorical variables are presented as the number and percentage. These variables were compared by overall valvular heart disease status using a Wilcoxon rank-sum test or Pearson χ² test for continuous and categorical variables, respectively. Kaplan–Meier event rate curves compare the primary efficacy and safety outcomes by valvular heart disease status and randomized treatment. The treatment effect of apixaban in comparison with warfarin was assessed by valvular heart disease status for all efficacy and safety outcomes using Cox proportional hazards models. The results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs) for apixaban versus warfarin among those with and without valvular heart disease; P values for the interaction of effect of randomized treatment and valvular heart disease status are provided. Proportional hazards assumptions were assessed for valvular heart disease status and for randomized treatment by plotting Schoenfeld residuals and assessing correlation over time; no violations were suggested. Analyses for the primary outcome and key secondary efficacy outcomes included all patients for whom valvular heart disease status was known and were analyzed by randomized treatment group. The safety outcome analysis included all patients who received at least 1 dose of study medication.

Among the subgroup of patients with valvular heart disease, we further evaluated treatment interactions with valve location (mitral, aortic, and tricuspid) for the primary efficacy and safety outcomes. Finally, to assess the sensitivity of the results to our definition of valvular heart disease, each outcome was evaluated in the same manner by using a definition that included any, including mild, valvular heart disease.

Role of the Funding Source
Bristol-Myers Squibb and Pfizer funded the ARISTOTLE trial and supported this analysis through a grant to Duke University. All analyses were conducted at the Duke Clinical Research Institute, and the authors had full access to all data through the Duke Clinical Research Institute. The authors are fully responsible for the study design, data collection, analysis and interpretation of the data, and writing of the manuscript. The sponsor played no role in the decision to submit the manuscript for publication.

Results
In ARISTOTLE, 18,201 patients with atrial fibrillation and at least 1 risk factor for stroke were randomly assigned and data on valvular heart disease status were available for 18,197 patients. Of these patients, 4,808 (26.4%) had a history of moderate or severe valvular heart disease or previous valve surgery. Of these 4,808 patients, 3,237 (67.3%) had a medical history of at least moderate valvular heart disease; 3,723 (77.4%) had baseline echocardiography data with at least moderate valvular heart disease; and 251 (5.2%) had previous valve surgery (Figure 1). The numbers of patients with specific valve lesions are described in Table 1. Importantly, the categories are not mutually exclusive. The majority of patients with valvular heart disease had mitral or tricuspid regurgitation; a smaller proportion had aortic stenosis, other valve lesions, or previous valve surgery. Patients randomly assigned to apixaban and warfarin had similar type and frequency of valvular heart disease (P>0.05 for all).

Baseline Characteristics
The baseline characteristics of patients with and without valvular heart disease are shown in Table 2. Patients with valvular heart disease were older; had more previous myocardial infarction, heart failure, prior bleeding, and renal impairment; had more persistent or permanent atrial fibrillation; had a higher mean CHADS2 score; and had less hypertension and diabetes mellitus than patients without valvular heart disease. Among patients with and without valvular heart disease, those randomly assigned to apixaban or warfarin had similar baseline characteristics (data not shown, P>0.05 for all).
Outcomes According to Valvular Heart Disease Status

Patients with valvular heart disease had higher rates of stroke or systemic embolism than patients without valvular heart disease (3.2% versus 2.4%; HR, 1.34; 95% CI, 1.10–1.62; \( P = 0.003 \)) and higher rates of death than patients without valvular heart disease (9.1% versus 6.2%; HR, 1.48; 95% CI, 1.32–1.67; \( P < 0.001 \)). Patients with valvular heart disease also tended to have higher rates of major bleeding than those without valvular heart disease; however, this difference was not statistically significant (4.6% versus 4.3%; HR, 1.11; 95% CI, 0.95–1.29; \( P = 0.21 \)).

Efficacy and Safety of Apixaban and Warfarin in Patient With and Without Valvular Heart Disease

Of the 13,389 patients without valvular heart disease, 6,681 were assigned to apixaban and 6,708 were assigned to warfarin. Of the 4,808 patients without valvular heart disease, 2,438 were assigned to apixaban and 2,370 were assigned to warfarin. Kaplan–Meier curves for the primary efficacy and safety outcomes by randomized treatment group and valvular heart disease status are shown in Figures 2 and 3. The benefits of apixaban in comparison with warfarin in reducing stroke or systemic embolism were consistent in patients with (HR, 0.70; 95% CI, 0.51–0.97) and without (HR, 0.84; 95% CI, 0.67–1.04) valvular heart disease (interaction \( P \) value=0.38). Other efficacy outcomes, including stroke, ischemic stroke, hemorrhagic stroke, death from any cause, and several composite outcomes were consistently and similarly reduced with apixaban in comparison with warfarin (Figure 4).

The benefits of apixaban in comparison with warfarin in causing less major bleeding were also consistent in patients with (HR, 0.79; 95% CI, 0.61–1.04) and without (HR, 0.65; 95% CI, 0.55–0.77) valvular heart disease (interaction \( P \) value=0.23). Similarly, consistent results were seen for other bleeding outcomes including intracranial bleeding, major or clinically relevant nonmajor bleeding, and any bleeding (Figure 5).

Mitral and Aortic Valve Locations

Analysis by valve location is shown in Table 3. Patients with mitral valve disease had consistent benefits of apixaban over warfarin for stroke or systemic embolism and major bleeding. Similarly, patients with aortic valve disease had consistent benefits of apixaban over warfarin for stroke or systemic embolism and major bleeding.

Table 1. Types of Valvular Heart Disease

<table>
<thead>
<tr>
<th>Any VHD*</th>
<th>Overall</th>
<th>Apixaban</th>
<th>Warfarin</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any mitral valve disease</td>
<td>3578</td>
<td>74.4</td>
<td>1801</td>
<td>73.9</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>3526</td>
<td>73.3</td>
<td>1778</td>
<td>72.9</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>131</td>
<td>2.7</td>
<td>69</td>
<td>2.8</td>
</tr>
<tr>
<td>Any aortic valve disease</td>
<td>1150</td>
<td>23.9</td>
<td>604</td>
<td>24.8</td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td>887</td>
<td>18.4</td>
<td>462</td>
<td>19.0</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>384</td>
<td>8.0</td>
<td>208</td>
<td>8.5</td>
</tr>
<tr>
<td>Tricuspid regurgitation</td>
<td>2124</td>
<td>44.2</td>
<td>1082</td>
<td>44.4</td>
</tr>
<tr>
<td>Previous valve surgery</td>
<td>251</td>
<td>5.2</td>
<td>132</td>
<td>5.4</td>
</tr>
</tbody>
</table>

VHD indicates valvular heart disease.

*Patients may have more than one type of valvular heart disease.
benefits of apixaban over warfarin for stroke or systemic embolism and for major bleeding. Similar benefits of apixaban in comparison with warfarin were also seen in patients with tricuspid valve disease and in patients with previous valve surgery (data not shown).

Sensitivity Analyses
When we included mild valvular heart disease by baseline echocardiography, 10,809 patients (59.4%) had valvular heart disease at baseline (Table 4). Consistent effects of apixaban in comparison with warfarin were seen in patients with and without at least mild valvular heart disease for stroke or systemic embolism, hemorrhagic stroke, death, and bleeding outcomes. Analysis exploring interactions by treatment and valvular heart disease severity were performed, and the results across the gradient of valve disease severity were similar to the main analysis for both the primary efficacy (interaction \( P \) value=0.90) and safety (interaction \( P \) value=0.67) outcomes.

Discussion
In this analysis from the ARISTOTLE trial, we found that more than a quarter of patients with nonvalvular atrial fibrillation and an indication for oral anticoagulation have moderate or severe valvular heart disease. In this context, nonvalvular is
a misnomer and may be misleading. Patients with atrial fibrillation and valvular heart disease are at higher risk for stroke and systemic embolism and bleeding than patients without valvular heart disease and may derive particular benefit from oral anticoagulation.

Valvular heart disease is common in both developed and developing countries and imposes a huge burden on limited healthcare resources. In comparison with other cardiovascular diseases, there are few randomized clinical trials evaluating the effects of medical intervention in patients with valvular heart disease. Structural changes from the pressure and volume overload alter the electrophysiological properties of the left atrium, and the rheumatic process itself may lead to atrial fibrosis which may partially explain the occurrence of atrial fibrillation in patients with valvular heart disease. Adjusting for other relevant conditions, valvular heart disease is associated with a 1.8- to 3.4-fold higher risk of atrial fibrillation in men and women, respectively. Although many patients develop atrial fibrillation as the result of valvular heart disease, there are concomitant factors that may contribute to the occurrence of atrial fibrillation, such as older age, heart failure, hypertension, coronary artery disease, and diabetes mellitus. In the current analysis, we found that patients with valvular heart disease were older; had more previous myocardial

![Stroke or Systemic Embolism](image1)

**Figure 2.** Kaplan–Meier estimates. Stroke or systemic embolism in patients with and without valvular heart disease by treatment assignment. VHD indicates valvular heart disease.

<table>
<thead>
<tr>
<th>No. at Risk:</th>
<th>NoVHD, Apixaban</th>
<th>NoVHD, Warfarin</th>
<th>VHD, Apixaban</th>
<th>VHD, Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>NoVHD, Apixaban</td>
<td>6681</td>
<td>6430</td>
<td>6253</td>
<td>4534</td>
</tr>
<tr>
<td>NoVHD, Warfarin</td>
<td>6708</td>
<td>6398</td>
<td>6207</td>
<td>4494</td>
</tr>
<tr>
<td>VHD, Apixaban</td>
<td>2438</td>
<td>2305</td>
<td>2222</td>
<td>1573</td>
</tr>
<tr>
<td>VHD, Warfarin</td>
<td>2370</td>
<td>2228</td>
<td>2138</td>
<td>1547</td>
</tr>
</tbody>
</table>

![ISTH Major Bleeding](image2)

**Figure 3.** Kaplan–Meier estimates. Major bleeding in patients with and without valvular heart disease by treatment assignment. ISTH indicates International Society on Thrombosis and Haemostasis; and VHD, valvular heart disease.

<table>
<thead>
<tr>
<th>No. at Risk:</th>
<th>NoVHD, Apixaban</th>
<th>NoVHD, Warfarin</th>
<th>VHD, Apixaban</th>
<th>VHD, Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>NoVHD, Apixaban</td>
<td>6659</td>
<td>5989</td>
<td>5610</td>
<td>4130</td>
</tr>
<tr>
<td>NoVHD, Warfarin</td>
<td>6691</td>
<td>5911</td>
<td>5512</td>
<td>3997</td>
</tr>
<tr>
<td>VHD, Apixaban</td>
<td>2428</td>
<td>2131</td>
<td>1974</td>
<td>1391</td>
</tr>
<tr>
<td>VHD, Warfarin</td>
<td>2360</td>
<td>2515</td>
<td>1842</td>
<td>1333</td>
</tr>
</tbody>
</table>
infarction, bleeding, heart failure, and renal impairment; and higher CHADS2 score. These variables may also contribute to the higher rate of thromboembolic and bleeding events in patients with valvular heart disease. Patients with mitral valve disease may have higher left atrium volume, contributing to blood stasis and promoting thrombus formation and leading to higher rates of thromboembolic events.18 Among patients with valvular heart disease, age, atrial fibrillation, and aortic stenosis are independent predictors of cerebrovascular events.5 In the ARISTOTLE study, detailed echocardiographic information on valvular heart disease severity was not collected, and classification of valvular lesion and severity relied on clinical data collected in the case report forms. Patients with clinically significant (moderate to severe) mitral stenosis and those with mechanical prosthetic heart valves were excluded; however, patients with any other form of valvular heart disease including mild mitral stenosis, mitral regurgitation, aortic stenosis or regurgitation, tricuspid valve disease, and previous valve surgery were included. Despite the population being characterized as having nonvalvular atrial fibrillation, these data confirm that apixaban, in comparison with warfarin, resulted in reductions in stroke or systemic embolism, caused less bleeding, and reduced mortality similarly in patients with and without valvular heart disease.

Patients with clinically significant (moderate or severe) mitral stenosis were excluded because ARISTOTLE was designed as a noninferiority trial. The noninferiority margin for ARISTOTLE was based on the previous systematic review of 6 clinical trials that compared warfarin and placebo in patients with nonvalvular atrial fibrillation.9 These trials excluded patients with mitral stenosis because, when they were conducted, warfarin was already established to be effective for thromboembolism prophylaxis in these patients who are at such high risk of stroke without treatment that assignment to control was considered unethical.10 Based on the constancy assumption that is fundamental to noninferiority analyses, the ARISTOTLE trial excluded patients with clinically significant mitral stenosis. There is no reason to think that apixaban would not be effective for stroke prevention in patients with clinically important mitral stenosis; however, before its use can be recommended, additional randomized data in patients with rheumatic mitral stenosis are needed.

Patients with other indications for warfarin therapy, including mechanical prosthetic heart valves, were excluded from the ARISTOTLE trial. Recently, the Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etxetil in Patients after Heart Valve Replacement (RE-ALIGN)19 study comparing dabigatran with dose-adjusted warfarin evaluated patients who had undergone aortic or mitral valve replacement within the past 7 days and those who had undergone such replacement at least 4 months earlier. The trial was terminated prematurely because of an excess of thromboembolic and bleeding events among patients in the dabigatran group. The mechanism of risk for patients with mechanical heart valves may...
be substantially different from those with atrial fibrillation and may require different antithrombotic strategies. A total of 251 patients with previous valve surgery (bioprosthetic heart valve or valve repair) were enrolled in ARISTOTLE and are included in this analysis. Unfortunately, however, details of their valve surgery were not collected. Whether or not apixaban is safe and effective in patients with previous bioprosthetic valve surgery will likely also require additional randomized data.

One quarter of the ARISTOTLE population had moderate or severe valvular abnormalities; therefore, the term nonvalvular atrial fibrillation is a misnomer. A more appropriate description should be pursued to reflect the clinical characteristics of those patients included in trials of new oral anticoagulation agents. With the exception of those patients with mitral stenosis and with mechanical prosthetic heart valves, patients with valvular heart disease and atrial fibrillation are an important cohort of patients that could benefit from increased use of the new oral anticoagulants. The current labeling and description of these new oral anticoagulants as being indicated for nonvalvular atrial fibrillation is a misnomer. A more appropriate description should be pursued to reflect the clinical characteristics of those patients included in trials of new oral anticoagulation agents.

### Limitations

This subgroup analysis in patients with and without valvular heart disease was not prespecified. Although a substantial portion of the population had valve disease, there may be a lack of statistical power to detect heterogeneity in the effects of apixaban versus warfarin. Valvular heart disease was defined clinically without standardized core laboratory verification. This can be viewed as a weakness or a strength because this is how valvular heart disease is assessed clinically. There was no information on the etiology of valvular heart disease and, for those with previous valve surgery, the

### Table 3. Apixaban Versus Warfarin in Patients With Mitral and Aortic Valvular Heart Disease

<table>
<thead>
<tr>
<th></th>
<th>Rate %/y (No. of Events)</th>
<th>Apixaban</th>
<th>Warfarin</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mitral VHD</strong></td>
<td>(n=1801)</td>
<td>(n=1777)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or SE</td>
<td>1.32 (43)</td>
<td>1.89 (61)</td>
<td>0.70 (0.47–1.04)</td>
<td></td>
</tr>
<tr>
<td>ISTM major bleeding</td>
<td>2.12 (63)</td>
<td>2.94 (84)</td>
<td>0.72 (0.52–1.00)</td>
<td></td>
</tr>
<tr>
<td><strong>Aortic VHD</strong></td>
<td>(n=604)</td>
<td>(n=546)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or SE</td>
<td>1.57 (17)</td>
<td>2.88 (27)</td>
<td>0.55 (0.30–1.01)</td>
<td></td>
</tr>
<tr>
<td>ISTM major bleeding</td>
<td>2.98 (29)</td>
<td>4.21 (34)</td>
<td>0.72 (0.44–1.18)</td>
<td></td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; ISTM, International Society on Thrombosis and Haemostasis; SE, systemic embolism; and VHD, valvular heart disease.

*HR (95% CI) for apixaban versus warfarin.

### Table 4. Effect of Apixaban Versus Warfarin by Valvular Heart Disease Status, Including Mild Valvular Heart Disease

<table>
<thead>
<tr>
<th></th>
<th>Rate %/y (No. of Events)</th>
<th>Apixaban</th>
<th>Warfarin</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No VHD</strong></td>
<td>(N=7388)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or SE</td>
<td>1.20 (82)</td>
<td>1.41 (95)</td>
<td>0.85 (0.64–1.15)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.23 (16)</td>
<td>0.41 (28)</td>
<td>0.56 (0.31–1.04)</td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>3.21 (224)</td>
<td>3.91 (270)</td>
<td>0.82 (0.69–0.98)</td>
<td></td>
</tr>
<tr>
<td><strong>VHD</strong></td>
<td>(N=10809)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or SE</td>
<td>1.31 (130)</td>
<td>1.73 (170)</td>
<td>0.76 (0.60–0.95)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.24 (24)</td>
<td>0.50 (50)</td>
<td>0.48 (0.29–0.78)</td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>3.74 (379)</td>
<td>3.96 (399)</td>
<td>0.95 (0.82–1.09)</td>
<td></td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; ISTM, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; CRNM, clinically relevant nonmajor; SE, systemic embolism; and VHD, valvular heart disease.

*HR (95% CI) for apixaban vs warfarin.

†P value for the randomized treatment by valvular heart disease status interaction.
type of surgery—bioprosthetic valve replacement versus valve repair—is unknown.

**Conclusions**

In a large contemporary clinical trial in patients with atrial fibrillation and an indication for oral anticoagulation, over a quarter of patients have a history of moderate or severe valvular heart disease or previous valvular surgery. The coexistence of atrial fibrillation and valvular heart disease is associated with a higher risk of thromboembolic events and bleeding. There was no evidence of a differential effect of apixaban over warfarin in patients with and without valvular heart disease in reducing stroke and systemic embolism, causing less major bleeding, and reducing mortality. With the exception of those with clinically significant mitral stenosis or mechanical prosthetic heart valves, apixaban is an attractive alternative to warfarin in patients with atrial fibrillation and valvular heart disease.

**Acknowledgments**

Elizabeth Cook of the Duke Clinical Research Institute provided editorial assistance.

**Sources of Funding**

The ARISTOTLE trial was supported by Bristol-Myers Squibb and Pfizer.

**Disclosures**

Dr Avezum reports consulting and advisory board fees from Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer. Dr Lopes reports institutional research grants from Bristol-Myers Squibb, Pfizer, and GlaxoSmithKline; and consulting/honoraria from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer. Dr Hanna is an employee of Bristol-Myers Squibb. Dr Pais reports a research grant from AstraZeneca. Dr De Caterina reports research grants and consulting fees/honoraria from Bristol-Myers Squibb, Pfizer, and Daiichi-Sankyo. Dr Goto reports research grants from Pfizer, and honoraria from Bristol-Myers Squibb. Dr Alexander reports institutional research grants from Bristol-Myers Squibb and Pfizer; and consulting fees/honoraria from Bristol-Myers Squibb, Pfizer, and Sanofi. Dr Granger reports research grants from Sanofi-Aventis, Astellas, and the Medicines Company; consulting fees/honoraria from Boehringer Ingelheim, Pfizer, and Astellas. Dr Avezum reports no conflicts.

**References**


The coexistence of atrial fibrillation and valvular heart disease (VHD) is associated with a higher risk of thromboembolic events and bleeding. There is a lack of available data evaluating new oral anticoagulants in patients with VHD and atrial fibrillation. We compared the effect of apixaban and warfarin on rates of stroke or systemic embolism, major bleeding, and death in 4808 patients with and without moderate or severe VHD, from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study. Apixaban, in comparison with warfarin, had similar relative and larger absolute benefits in reducing stroke or systemic embolism, causing less bleeding, and reducing mortality in patients with VHD in comparison with those without VHD. The current analysis provides a reliable evaluation of the efficacy and safety of apixaban in patients with VHD, and the results will potentially improve the cardiovascular burden of atrial fibrillation in VHD.
Apixaban in Comparison With Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: Findings From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial


_Circulation_. 2015;132:624-632; originally published online June 23, 2015;
doi: 10.1161/CIRCULATIONAHA.114.014807

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/132/8/624

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2016/12/29/CIRCULATIONAHA.114.014807.DC1

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints:** Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/
Apixaban, 승모판막 협착증을 제외한 다른 판막성 심방세동 환자에서도 비판막성 심방세동 환자에서와 동등한 효과를 보였다: ARISTOTLE 연구의 하위분석

최기준 교수 서울아산병원 심장내과

초록

배경
Apixaban은 비판막성 심방세동 환자에서 뇌졸중과 전신 색전증의 예방 효과로 승인을 받았다. 그러나 apixaban을 이용한 ARISTOTLE(Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) 연구에는 임상적으로 의미 있는 승모판막 협착증과 기계판막 환자만 제외하였고, 상당수의 다른 판막질환 환자들이 포함되어 있었다.

방법 및 결과
본 연구에서는 중등도 혹은 심한 판막성 심방세동 환자와 그렇지 않은 심방세동 환자에서 apixaban과 외파란의 뇌졸중, 전신 색전증, 주요 출혈 및 사망률의 발생률을 Cox proportional hazards 모델링 방법을 이용하여 비교하였다. ARISTOTLE에 등록된 18,201명의 환자 중 4,808명(26.4%)이 중등도 이상의 판막질환이나 과거 판막수술(생체판막수술이나 판막성형술)의 병력을 갖고 있었다. 판막질환 환자군은 판막질환을 갖고 있지 않은 환자군에 비해 뇌졸중이나 전신 색전증 및 출혈 모두 높은 발생률을 보였다. 외파란에 대한 apixaban의 효과는 다음 사건의 발생률에 있어 판막질환 환자군과 판막질환을 갖고 있지 않은 환자군에서 대등한 차이를 보이지 않았다: 뇌졸중과 전신 색전증의 감소(HR, 0.79; 95% CI, 0.67–1.04; interaction P=0.38), 주요 출혈의 감소(HR, 0.70; 95% CI, 0.51–0.97 vs. HR, 0.84; 95% CI, 0.67–1.04; interaction P=0.23), 사망률의 감소(HR, 1.01; 95% CI, 0.84–1.22 vs. HR, 0.84; 95% CI, 0.73–0.96; interaction P=0.10).

결론
비판막성 심방세동 환자들을 대상으로 한 ARISTOTLE 연구에서 1/4 이상의 환자들이 중등도 혹은 심한 판막성 질환을 갖고 있었다. 판막질환 환자군과 판막질환을 갖고 있지 않은 환자군에서 외파란에 대한 apixaban의 효과는 뇌졸중과 전신 색전증의 감소, 주요 출혈의 감소, 사망률의 감소에 있어 두드러진 차이를 보이지 않았다.

Arrhythmia 47