Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: results from the ARISTOTLE trial

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Aims
It is uncertain whether the benefit from apixaban varies by type and duration of atrial fibrillation (AF).

Methods and results
A total of 18,201 patients with AF [2786 (15.3%) with paroxysmal and 15,412 (84.7%) with persistent or permanent] were randomized to apixaban or warfarin. In this pre-specified secondary analysis, we compared outcomes and treatment effect of apixaban vs. warfarin by AF type and duration. The primary efficacy endpoint was a composite of ischaemic or haemorrhagic stroke or systemic embolism. The secondary efficacy endpoint was all-cause mortality. There was a consistent reduction in stroke or systemic embolism (P for interaction = 0.71), all-cause mortality (P for interaction = 0.75), and major bleeding (P for interaction = 0.50) with apixaban compared with warfarin for both AF types. Apixaban was superior to warfarin in all studied endpoints, regardless of AF duration at study entry (P for all interactions >0.13). The rate of stroke or systemic embolism was significantly higher in patients with persistent or permanent AF than patients with paroxysmal AF (1.52 vs. 0.98%; P = 0.003, adjusted P = 0.015). There was also a trend towards higher mortality in patients with persistent or permanent AF (3.90 vs. 2.81%; P = 0.0002, adjusted P = 0.066).

Conclusion
The risks of stroke, mortality, and major bleeding were lower with apixaban than warfarin regardless of AF type and duration. Although the risk of stroke or systemic embolism was lower in paroxysmal than persistent or permanent AF, apixaban is an attractive alternative to warfarin in patients with AF and at least one other risk factor for stroke, regardless of the type or duration of AF.

Keywords
Paroxysmal atrial fibrillation • Persistent atrial fibrillation • Permanent atrial fibrillation • Apixaban • Stroke • Major bleeding

Introduction
One of the most serious complications of atrial fibrillation (AF) is stroke. Not only is stroke prevalent in patients with AF, but when it occurs, it is either fatal or associated with substantial disability in the majority of patients. Whether the risk of stroke is affected by the type, duration, and frequency of AF has been debated for years. Although a few studies have suggested a lower risk of stroke in patients with paroxysmal AF than those with persistent or permanent AF, a pooled analysis of the Stroke Prevention in Atrial Fibrillation (SPAF) trials demonstrated a comparable risk of stroke in paroxysmal and permanent AF.6–8 Practice guidelines on AF management made identical recommendations regarding stroke prevention for all types of AF, based on known risk
Factors for stroke in this patient population.10 These recommendations are further supported by data from the Euro Heart Survey and a pooled analysis of the SPORTIF (Stroke Prevention with the Oral Thrombin Inhibitor in Atrial Fibrillation) III and V randomized clinical trials that showed a similar risk of stroke in paroxysmal AF and persistent or permanent AF.11,12

Until recently, oral anticoagulation with vitamin K antagonists (e.g., warfarin) was the only effective treatment available for stroke prevention in AF. Over the past few years, several new oral anticoagulants that specifically inhibit thrombin or factor Xa have emerged.13–16 In the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thrombo-embolic Events in Atrial Fibrillation) trial, apixaban was superior to warfarin at reducing the risk of stroke or systemic embolism, bleeding, and mortality in patients with AF and at least one risk factor for stroke or systemic embolism.14,17 Whether the effect of apixaban varies by type and duration of AF is uncertain. We conducted this pre-specified secondary analysis of the ARISTOTLE trial to compare outcomes and treatment effect of apixaban vs. warfarin by AF type and duration.

Methods

The ARISTOTLE trial

The details of the ARISTOTLE trial have been published.14,17 In brief, ARISTOTLE was a multicentre, double-blind, double-dummy clinical trial that randomized patients with AF and at least one risk factor for thrombo-embolism as determined by the CHADS2 score to dose-adjusted warfarin and apixaban placebo (n = 9081) vs. apixaban and warfarin placebo (n = 9120). The primary objective of the trial was to study whether apixaban is non-inferior to warfarin at reducing the risk of stroke or systemic embolism. If non-inferiority is demonstrated, the trial was powered to detect superiority of apixaban over warfarin in its effect on stroke or systemic embolism followed by bleeding followed by mortality.14,17

Patient population

To be eligible for the trial, patients had to be in AF or atrial flutter documented on two separate occasions at least 2 weeks apart in the 6 months prior to enrolment. Atrial fibrillation or atrial flutter may be documented by an electrocardiogram (ECG) or as an episode at least 1 min in duration on a rhythm strip of a Holter recording. In addition, patients had to have at least one of the following risk factors for stroke: age ≥ 75 years; prior stroke, transient ischaemic attack (TIA), or systemic embolism; symptomatic heart failure within 3 months or left ventricular ejection fraction ≤ 40%; diabetes mellitus; and hypertension requiring pharmacological treatment. Patients were ineligible for enrolment if they had moderate or severe mitral stenosis, AF due to a reversible cause, a contraindication to oral anticoagulation due to an increased bleeding risk, conditions other than AF that required anticoagulation such as prosthetic heart valve, persistent uncontrolled hypertension, or planned AF or atrial flutter ablation among other criteria listed in the original manuscript.14,17

The definitions of paroxysmal, persistent, and permanent AF used in the trial were in accordance with the definitions used in the 2006 American College of Cardiology/American Heart Association/European Society of Cardiology AF guidelines.9 Specifically, paroxysmal AF was defined as recurrent AF that terminates spontaneously, persistent AF was defined as AF that is sustained beyond 7 days, and permanent AF was defined as long-standing AF in which restoring and/or maintaining sinus rhythm has failed or has been foregone. The prior need for a cardioversion did not automatically lead to classifying AF as persistent; the subsequent occurrence of self-terminating paroxysms of AF in such patients led to classifying them as having paroxysmal AF. The type of AF was classified by the sites at randomization when they had to specify whether a particular patient had paroxysmal or persistent/permanent (combined into one category) AF or atrial flutter documented by an ECG at the time of enrolment or whether a patient had AF or atrial flutter documented on two separate occasions at least 2 weeks apart in the 6 months prior to enrolment.

Treatment

Apixaban or matching placebo was given twice daily with apixaban administered in 5 mg pills, or 2.5 mg doses for patients with two or more of the following factors: age ≥ 80 years, body weight < 60 kg, and serum creatinine ≥ 1.5 mg/dL (133 µmol/L). Warfarin (or matching placebo) was administered in 2 mg tablets and was adjusted to achieve a target international normalized ratio (INR) of 2.0–3.0. International normalized ratios were monitored using a blinded, encrypted, point-of-care INR device. For patients who were lost to follow-up or withdrew consent, attempts were made to ascertain vital status at the end of the trial. The median time in therapeutic range (TTR) among patients on warfarin was 66.0% and the mean time was 62.2%. Therapies for rate and rhythm control were left to the discretion of the treating physician.14,17

In this analysis, rhythm control during the follow-up was defined as the use of an antiarrhythmic medication, cardioversion, and/or ablation procedure for AF at any point during the study. Rate control was defined as the use of none of the above and use of beta-blockers, calcium channel blockers, and/or digoxin.

Endpoints

Using pre-specified criteria, all endpoints were adjudicated by clinical events committee blinded to treatment assignment.14,15 The primary efficacy endpoint for this analysis was a composite of ischaemic or haemorrhagic stroke or systemic embolism. Stroke was defined as a non-traumatic, focal neurological deficit of at least 24 h duration and was classified as ischaemic (with or without haemorrhagic transformation), haemorrhagic, or uncertain type (for patients without brain imaging or autopsy). The secondary efficacy endpoint was all-cause mortality.14,17

The primary safety endpoint for this analysis was International Society of Thrombosis and Hemostasis (ISTH) major bleeding. Per the ISTH criteria, major bleeding was defined as clinically overt bleeding accompanied by a decrease in the haemoglobin level of ≥ 2 g/dL, transfusion of ≥ 2 units of packed red blood cells, occurring in a critical site, or resulting in death.

Statistical analysis

Continuous variables are presented as means and standard deviations as well as medians and 25 and 75th percentiles, and categorical variables are presented as percentages. We examined the baseline characteristics of patients by type of AF and compared the two groups using t-tests for continuous variables and the χ2 tests for categorical variables.

For each type of AF at baseline, we determined the frequency of follow-up ECGs and calculated the proportion of patients with AF on all subsequent ECGs and no documentation of sinus rhythm. Subjects with no ECG during the follow-up (< 10%) were excluded from this subanalysis. We also calculated the proportion of patients in AF...
Baseline characteristics

At study entry, 2786 (15.3%) patients had paroxysmal AF and 15 412 (84.7%) had persistent or permanent AF. The median duration of AF prior to study entry for the overall population was 840 days (25th, 75th percentiles: 140, 2269); 489 (145, 1721) for patients with paroxysmal AF, and 914 (139, 2372) for patients with persistent or permanent AF. The baseline characteristics by type of AF are presented in Table 1. New onset AF within 14 days before randomization was present in 31 (1.1%) patients with paroxysmal AF and 824 (5.4%) patients with persistent or permanent AF. Compared with patients with paroxysmal AF, those with persistent or permanent AF were older and were less often women, more often had a history of heart failure and a higher CHADS2 score, and less often had a history of prior myocardial infarction, hypertension, and vascular disease. There was a trend towards a higher rate of prior stroke, TIA, or systemic embolism among patients with paroxysmal AF. Prior clinically relevant or spontaneous bleeding was evenly distributed between the two groups.

Treatment

Of patients with paroxysmal AF, 1347 (7.55%) were randomized to apixaban and 1412 (7.76%) to warfarin. Of patients with persistent or permanent AF, 7744 (42.55%) were randomized to apixaban and 7668 (42.14%) to warfarin. Of patients with paroxysmal AF, 47.9% were vitamin K antagonist-naive vs. 41.9% of patients with persistent or permanent AF. In the warfarin group, patients with paroxysmal AF had a mean TTR of 61.7 and a median TTR of 65.0 and patients with persistent or permanent AF had a mean TTR of 62.3 and a median TTR of 66.0 during the trial (P-value for difference of means = 0.30).

Table 1 shows medications and procedures by type of AF at baseline. Compared with patients with paroxysmal AF, those with persistent or permanent AF less often received amiodarone, any antiarrhythmic medication, aspirin, clopidogrel, and statins. Patients with persistent or permanent AF more often received a beta-blocker, digoxin, and warfarin. The use of an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker and a calcium channel blocker was evenly distributed between the two groups. Patients with paroxysmal AF more often had a prior history of electrical cardioversion and AF ablation. During the follow-up, 627 (22.5%) patients with paroxysmal AF were managed with rhythm control and 2158 (77.5%) were managed with rate control. Of patients with persistent or permanent AF, 1020 (6.6%) were managed with rhythm control and 14391 (93.4%) were managed with rate control.

Outcomes

As shown in Figure 1, there was a consistent reduction in stroke or systemic embolism (P for interaction 0.71), all-cause mortality (P for interaction 0.75), and major bleeding (P for interaction 0.50) with apixaban compared with warfarin for both types of
Longer duration of AF was associated with a piecewise linear reduction in the risk of death \(P\)-value for death \(0.001\); HR: 0.83, 95% CI (0.76, 0.90) per 1 year increase in duration between 0–2 years; HR: 1.01, 95% CI (0.99, 1.04) beyond 2 years. There was no association between AF duration and any other endpoint. This association was sustained after controlling for age \(P\)-value \(0.001\). The benefit from apixaban was consistent compared with warfarin in all of the studied endpoints, regardless of the duration of AF at study entry \(P\)-value for all interactions \(0.13\).

As shown in Table 2 and Figure 2, the rates of stroke or systemic embolism, all-cause mortality, and the composite endpoint of stroke or systemic embolism, all-cause mortality, and major bleeding were significantly lower in patients with paroxysmal AF than patients with persistent or permanent AF [HR: 0.65, 95% CI (0.48, 0.87), \(P = 0.003\); HR: 0.72, (95% CI 0.61, 0.85), \(P = 0.002\); HR: 0.77, (95% CI: 0.68, 0.87), \(P < 0.0001\), respectively]. There was also a trend towards a lower risk of major bleeding in the paroxysmal AF group [HR: 0.83, 95% CI (0.68, 1.02), \(P = 0.078\)]. Adjusting for potential confounders, the risk of stroke or systemic embolism was still significantly lower for paroxysmal AF than for persistent or permanent AF [HR: 0.70, 95% CI (0.51, 0.93), \(P = 0.015\)]. There was a trend towards a higher risk of all-cause mortality and the composite endpoint of stroke or systemic embolism, all-cause mortality, and major bleeding in patients with persistent or permanent AF \(P = 0.066\) and \(P = 0.068\), respectively.

### Table 1  Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Paroxysmal AF ((n = 2786))</th>
<th>Persistent or permanent AF ((n = 15 412))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (25th, 75th), years</td>
<td>69 (61, 75)</td>
<td>70 (63, 76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>1166 (41.9)</td>
<td>5249 (34.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time from first documented occurrence of AF to randomization, mean (SD), months</td>
<td>39.7 (33.3)</td>
<td>52.4 (62.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median (25th, 75th)</td>
<td>16.0 (48, 56.5)</td>
<td>30.0 (46, 77.9)</td>
<td></td>
</tr>
<tr>
<td>New onset AF within 14 days before randomization, n (%)</td>
<td>31 (1.1)</td>
<td>824 (5.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP, mean (SD), mmHg</td>
<td>132 (16)</td>
<td>131 (16)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP, mean (SD), mmHg</td>
<td>78 (9)</td>
<td>79 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>84.3 (19.5)</td>
<td>84.0 (20.9)</td>
<td>0.504</td>
</tr>
<tr>
<td>Prior MI, n (%)</td>
<td>444 (15.9)</td>
<td>2141 (13.9)</td>
<td>0.005</td>
</tr>
<tr>
<td>Chronic heart failure, n (%)</td>
<td>680 (24.4)</td>
<td>4897 (31.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior stroke, TIA, or systemic embolism, n (%)</td>
<td>578 (20.7)</td>
<td>2959 (19.2)</td>
<td>0.058</td>
</tr>
<tr>
<td>Diabetess, n (%)</td>
<td>659 (23.7)</td>
<td>3887 (25.2)</td>
<td>0.079</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>2509 (90.1)</td>
<td>13 405 (87.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of vascular disease, n (%)</td>
<td>783 (28.10)</td>
<td>3717 (24.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior clinically relevant or spontaneous bleeding, n (%)</td>
<td>442 (15.9)</td>
<td>2598 (16.9)</td>
<td>0.200</td>
</tr>
<tr>
<td>Warfarin naive, n (%)</td>
<td>1334 (47.9)</td>
<td>6465 (41.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHADS2 score, mean (SD)</td>
<td>2.0 (1.1)</td>
<td>2.1 (1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHADS2 score, n (%)</td>
<td>1070 (38.4)</td>
<td>5112 (33.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Therapies at time of randomization, n (%)</td>
<td>928 (33.3)</td>
<td>5587 (36.3)</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>1975 (72.2)</td>
<td>10 855 (71.6)</td>
<td>0.507</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>1598 (58.4)</td>
<td>9884 (65.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin</td>
<td>978 (35.1)</td>
<td>4654 (30.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>65 (2.3)</td>
<td>272 (1.8)</td>
<td>0.041</td>
</tr>
<tr>
<td>Digoxin</td>
<td>341 (12.5)</td>
<td>5487 (36.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>834 (30.5)</td>
<td>4731 (31.2)</td>
<td>0.461</td>
</tr>
<tr>
<td>Statins</td>
<td>1299 (47.5)</td>
<td>6173 (40.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antiarrhythmic medications</td>
<td>1326 (48.5)</td>
<td>1876 (12.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior electrical cardioversion</td>
<td>695 (25.0)</td>
<td>2403 (15.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior AF ablation</td>
<td>62 (2.2)</td>
<td>216 (1.4)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BP, blood pressure; MI, myocardial infarction; SD, standard deviation; TIA, transient ischaemic attack.
Follow-up electrocardiogram data
The majority of patients had data entered on ≤2 ECGs during the follow-up; 10,696 (69.4%) in the persistent or permanent AF group and 1877 (67.4%) in the paroxysmal AF group. The proportion of patients with AF on all subsequent ECGs was 81.6% in the persistent or permanent AF group and 17.5% in the paroxysmal AF group (P < 0.0001). The proportion of patients in AF at the 1-year ECG was 87.8% in the persistent or permanent AF group vs. 23.6% on the paroxysmal AF group (P < 0.0001). Of patients with paroxysmal AF at study entry, 700 (30.9%) had AF on their last trial ECG; and of patients with persistent or permanent AF at study entry, 10,733 (87.3%) had AF on their last trial ECG.

Discussion
This study has three important findings. First, there was a consistent reduction in stroke or systemic embolism, all-cause mortality, and major bleeding with apixaban compared with warfarin regardless of the type of AF. Secondly, the superiority of apixaban over warfarin was consistent regardless of AF duration, defined as time from first documented occurrence of AF to randomization. Finally, in this study, persistent or permanent AF was associated with a higher risk of stroke or systemic embolism and a trend towards a higher risk of all-cause mortality than paroxysmal AF. These differences were maintained even after adjustment for differences in baseline characteristics that could influence the risk of these events.

Despite differences in baseline characteristics and outcomes by type of AF, there was a consistent reduction in stroke or systemic embolism, all-cause mortality, and major bleeding with apixaban compared with warfarin for both AF types. In an analysis of ACTIVE W (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events), compared with the combination of aspirin and clopidogrel, warfarin resulted in a lower risk of stroke or systemic embolism and a higher risk of bleeding, irrespective of the AF type.21 In RE-LY (Randomized Evaluation of
Long-Term Anticoagulation Therapy), and compared with warfarin, the higher studied dose of dabigatran showed superior efficacy for stroke prevention with comparable risk of major bleeding in patients with paroxysmal as well as patients with persistent and permanent AF. Thus, it seems likely that the results on stroke prevention with the new anticoagulants compared with warfarin will be consistent regardless of the type of AF.

In this study, apixaban was superior to warfarin, on average, and was consistent regardless of AF duration, defined as time from first documented occurrence of AF to randomization. To our knowledge, our study is the first to examine the effect of an anticoagulant by duration of AF in the context of a large, multicentre, randomized clinical trial. Similar analyses of ACTIVE W and RE-LY did not examine the benefit of study drug by duration of AF at study entry. Because of the potential clinical importance of this factor, it should be examined in future studies including secondary analyses of large contemporary clinical trials of AF. The association between longer duration of AF and reduction in the risk of death is intriguing; however, it likely reflects selection bias that resulted from inclusion in a clinical trial. In other words, patients with longer duration of AF have typically passed the initial first months of AF during which the risk of stroke and major bleeding is high and are more commonly warfarin experienced and more commonly had not had side-effects and complications on warfarin as such patients would have been excluded from participating in a randomized clinical trial.

Although some studies suggested lower event rates in patients with paroxysmal AF than patients with persistent or permanent AF, data from major clinical trials of warfarin as well as other anticoagulants failed to show any difference in clinical events related to AF by AF type. Our findings are in stark contrast with the findings of those studies and raise questions about potential reasons for these differences. Except for RE-LY, previous studies included substantially fewer patients than our study. Specificially, the pooled analysis of the SPAF trials included only 460 patients with paroxysmal AF and 1552 patients with sustained AF, the pooled analysis of the SPORTIF trials included 836 patients with paroxysmal AF and 6493 subjects with persistent AF, and the more recent ACTIVE W trial included 1202 patients with paroxysmal AF and 5495 subjects with persistent AF. By including more patients (2786 patients with paroxysmal AF and 15412 patients with persistent or permanent AF), our study had more statistical power to determine whether AF type is an independent risk factor for stroke or systemic embolism. Also, ARISTOTLE enrolled a greater proportion of patients with persistent/permanent AF than RE-LY (15412 vs. 12164). This may explain why our findings are different from the findings of RE-LY, as patients with persistent or permanent AF are typically more

**Figure 2** Outcomes by type of atrial fibrillation. (A) Stroke or systemic embolism. (B) Major bleeding. (C) All-cause mortality. (D) the composite endpoint of stroke or systemic embolism, all-cause mortality, and major bleeding.
morbid than patients with paroxysmal AF.\textsuperscript{22} Although largely speculative, differences between our findings and those of RE-LY may relate to differences in patient characteristics, definitions of types of AF, and outcomes or overall management of patients. Analyses of outcomes by AF type in other large contemporary randomized clinical trials, such as ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) and ENGAGE-AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction Study 48), may help address this controversy.\textsuperscript{15,23}

Several caveats should be kept in mind when assessing our results. First, classifying AF is challenging especially given the nuances of the definitions of AF types and the transitioning of some patients from one type of AF to another at different time points. Secondly, although this was a pre-specified secondary analysis of the ARISTOTLE trial and several statistical models were used to adjust for confounding, residual confounding cannot be ruled out. However, our adjusted analysis was quite comprehensive, and therefore, our findings cannot be explained by imbalances in measured covariates. Although there may be unmeasured patient characteristics associated with type of AF that would explain the observed discrepancies, we adjusted for well-known comorbidities that are likely to influence outcomes. Thirdly, we were unable to analyse persistent and permanent AF separately because these were combined into one category during data collection. Because patients with these types of AF may be inherently different, combining them may have introduced some bias. In addition, the distinction between paroxysmal and non-paroxysmal AF is not always clear cut. Fourthly, because the majority of patients in our study had two or fewer ECGs reported in follow-up, these data could not be used to discern type of AF during the follow-up. However, it is somewhat reassuring that the proportion of patients with AF on all subsequent ECGs was substantially higher in the persistent/permanent AF group than in the paroxysmal AF group (81.6 vs. 17.5%). Fifthly, we were neither able to capture the persistent/permanent AF group than in the paroxysmal AF group with AF on all subsequent ECGs was substantially higher in the paroxysmal AF group than in the persistent/permanent AF group.

Conclusions
In conclusion, in patients with AF and at least one risk factor for stroke, the risk of stroke or systemic embolism, mortality, and major bleeding was lower with apixaban than with warfarin regardless of the AF type and duration. Therefore, although the risk of stroke or systemic embolism was lower in paroxysmal than persistent or permanent AF, it seems equally important to consider the use of apixaban as an alternative to warfarin regardless of AF type or duration.

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Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation