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Apixaban Superior to Warfarin for Prevention of SSE In Patients With AF: Results from ARISTOTLE

Written by Maria Vinall

"In patients with atrial fibrillation, apixaban is superior to warfarin in preventing stroke or systemic embolism, causes less bleeding, and results in lower mortality," said Christopher B. Granger, MD, Duke Clinical Research Center, Durham, North Carolina, USA, in his discussion of the primary results from the Apixaban for Reduction In STrOke and other ThromboemboLic Events in atrial fibrillation (ARISTOTLE) trial [NCT00412984].

Warfarin is highly effective for the prevention of stroke in patients with atrial fibrillation (AF), but it has several limitations, including significant drug and food interactions, a narrow therapeutic range, the need for anticoagulation monitoring, and heightened risk of bleeding. Apixaban is a novel oral direct factor Xa inhibitor with rapid absorption, a 12-hour half-life, and 25% renal elimination that has been shown to reduce the risk of stroke and systemic embolism (SSE) in patients with AF compared with aspirin [Connolly SJ et al. *N Engl J Med* 2011].

In this randomized, double-blind trial, apixaban (5 mg BID) was compared with warfarin (target INR 2.0 to 3.0) in 18,201 patients who were enrolled in 39 countries. Participants had AF and at least one additional risk factor for stroke (eg, age ≥75 years, previous stroke, transient ischemic attack [TIA], and SSE). Subjects had a median age of 70 years (interquartile range 63 to 76 years), and ~65% were male. The mean $CHADS_2$ score was 2.1 (±1.1), and ~15% of participants had moderately impaired renal function (estimated creatinine clearance 30 to 50 mg/dL). The primary analysis was a test for noninferiority for apixaban relative to warfarin at reducing all strokes or SEEs (upper limit of 95% CI <1.38 and upper limit of 99% CI <1.44). The rate of major bleeding (as defined by the International Society of Thrombosis and Hemostasis [ISTH]) was the primary safety outcome. Secondary analyses tested for the superiority of apixaban relative to warfarin with respect to all-cause mortality and for the primary outcome of SSE.

The median duration of follow-up was 1.8 years. The mean percentage of time in which the INR was in the 2.0 to 3.0 therapeutic range (TTR) was 62.2%, similar to the RE-LY trial with dabigatran. Significantly more subjects who were treated with warfarin discontinued treatment (27.5%) compared with the apixaban group (25.3%; p=0.001), although discontinuations due to an adverse event (AE) were similar (apixaban 7.6% vs warfarin 8.4%).

The annualized rates of the primary endpoint were 1.27% for apixaban versus 1.60% for warfarin (HR, 0.79; 95% CI, 0.66 to 0.95; p values <0.001 and 0.014 for noninferiority and superiority, respectively; Table 1). The benefits of apixaban were consistent across all major subgroups. Treatment with apixaban also significantly reduced the rates of major bleeding by 31% (p<0.001), intracranial hemorrhage by 58% (p=0.001), and all-cause mortality by 11% (p=0.047; Table 1). Hemorrhagic stroke was significantly reduced with apixaban (0.24%/year vs 0.47%/year; p<0.001); however, rates of ischemic stroke (0.97%/year vs 1.05%/year; p=0.42) and myocardial infarction (0.53%/year vs 0.61%/year; p=0.37) were similar between the treatment groups. Over the 22-month treatment period, the use of apixaban prevented 6 strokes, 15 major bleeds, and 8 deaths per 1000 patients who were treated compared with warfarin.

Table 1. Efficacy Outcomes.

Outcome	Apixaban (n=9120)*	Warfarin (n=9081)*	HR (95% CI)	p value
Primary outcome: SSE	1.27	1.60	0.79 (0.66 to 0.95)	0.01
Stroke	1.19	1.51	0.79 (0.65 to 0.95)	0.01
Ischemic or uncertain type of stroke	0.97	1.05	0.92 (0.74 to 1.13)	0.42
Hemorrhagic	0.24	0.47	0.51 (0.35 to 0.75)	<0.001
Systemic embolism	0.09	0.10	0.87 (0.44 to 1.75)	0.70
All-cause death	3.52	3.94	0.89 (0.80 to 0.998)	0.047
Other secondary outcomes				
Stroke, systemic embolism, or all-cause death	4.49	5.04	0.89 (0.81 to 0.98)	0.02
Myocardial infarction	0.53	0.61	0.88 (0.66 to 1.17)	0.37
SSE, myocardial infarction, or all-cause death	4.85	5.49	0.88 (0.80 to 0.97)	0.01
Pulmonary embolism or deep vein thrombosis	0.04	0.05	0.78 (0.29 to 2.10)	0.63

*Event rate - %/year; SSE=stroke, systolic embolism; Source: Granger CB, Alexander JH, McMurray JJV et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. Aug 28, 2011.

ISTH major bleeding was significantly reduced with apixaban (2.13%/year vs 3.09%/year; p<0.001; Table 2), with consistent reductions in GUSTO severe bleeding by 54% (p<0.001) and TIMI major bleeding by 43% (p<0.001; Table 2). There were two significant interactions in the subgroup analyses for safety, patients with diabetes and patients with normal renal function did not show a significant reduction in ISTH major bleeding with apixaban. With regard to other AEs, the rates of abnormal liver function tests and hepatic serious AEs were similar between the treatment groups.

Table 2. Bleeding Outcomes.

Outcome	Apixaban (n=9088)*	Warfarin (n=9052)*	HR (95% CI)	p value
Primary outcome: ISTH major bleeding	2.13	3.09	0.69 (0.60 to 0.80)	<0.001
Intracranial	0.33	0.80	0.42 (0.30 to 0.58)	<0.001
Gastrointestinal	0.76	0.86	0.89 (0.70 to 1.15)	0.37
Other locations	1.79	2.27	0.79 (0.68 to 0.93)	0.004
Major or clinically relevant nonmajor bleeding	4.07	6.01	0.68 (0.61 to 0.75)	<0.001
GUSTO severe bleeding	0.52	1.13	0.46 (0.35 to 0.60)	<0.001
GUSTO moderate or severe bleeding	1.29	2.18	0.60 (0.50 to 0.71)	<0.001
TIMI major bleeding	0.96	1.69	0.57 (0.46 to 0.70)	<0.001
TIMI major or minor bleeding	1.55	2.46	0.63 (0.54 to 0.75)	<0.001
Any bleeding	18.1	25.8	0.71 (0.68 to 0.75)	<0.001
Net clinical bleeding				
SSE or major bleeding	3.17	4.11	0.77 (0.69 to 0.86)	<0.001
SSE, major bleeding, or all-cause death	6.13	7.20	0.85 (0.78 to 0.92)	<0.001

*Event rate - %/year; ISTH=International Society of Thrombosis and Hemostasis; GUSTO=Global Use of Strategies to Open Occluded Coronary Arteries; TIMI=Thrombolysis in Myocardial Infarction, SSE=stroke, systemic embolism; Source: Granger CB, Alexander JH, McMurray JJV et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. Aug 28, 2011.

ARISTOTLE is the third recently completed Phase 3 trial that has compared a novel oral anticoagulant with warfarin in patients with AF. These findings are important, in that they represent the first double-blind trial that has demonstrated superiority of a novel oral anticoagulant over warfarin in terms of both efficacy and safety and a reduction in mortality. All three agents that have been tested to date (apixaban, rivaroxaban, and dabigatran) have demonstrated a favorable safety profile with a primary benefit of reducing intracranial bleeding compared with warfarin. Whether newer agents can further reduce ischemic/thrombotic stroke and how these novel drugs compare with warfarin managed with a higher TTR are two important unanswered questions. As more treatment options become available for patients with AF, clinicians and medical systems will need to carefully weigh their respective characteristics as well as cost-effectiveness. Head-to-head comparisons in terms of efficacy and safety are needed.

Further reading: Granger et al. *N Engl J Med* 2011.

Benefits of Apixaban over Warfarin are Consistent, Irrespective of TTR

Written by Maria Vinall

Results from the ARISTOTLE (Apixaban for Reduction In STrOke and other ThromboemboLic Events in atrial fibrillation [NCT00412984]) trial showed that treatment with apixaban results in a lower rate of stroke or systemic embolism (SSE), less bleeding, and lower mortality compared with warfarin therapy [Granger CB et al. *N Engl J Med* 2011]. Lars Wallentin, MD, Uppsala University, Uppsala, Sweden, discussed the results of a subanalysis of data from ARISTOTLE, which demonstrated that the benefit of apixaban over warfarin was not related to the quality of INR control at the individual ARISTOTLE study centers.

A total of 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke from 1034 centers in 39 countries were randomized to double-blind, double-dummy treatment with apixaban 5 mg BID versus warfarin (target INR 2.0 to 3.0). In the main trial results, both the primary efficacy outcome of SSE (HR, 0.79; 95% CI, 0.66 to 0.95; p=0.01) and the primary safety outcome of ISTH major bleeding (HR, 0.69; 95% CI, 0.60 to 0.80; p<0.001) were reduced with apixaban compared with warfarin. The purpose of the current analysis was to assess whether the benefits of apixaban were consistent among centers that achieved similar time-in-therapeutic range (TTR). Each center's TTR was calculated as the median of all individuals' TTRs in warfarin-treated patients and then assigned as a measure of quality of INR control for all patients. Analyses were adjusted for differences in baseline variables with the potential to influence TTR and/or outcome (eg, age, sex, body weight, $CHADS_2$ score, prior stroke, diabetes mellitus, hypertension, heart failure, and baseline medications).

Consistent with the main trial results, when stratified by the centers' TTRs, there was a directionally consistent reduction in the primary endpoint with apixaban compared with warfarin in each stratum (Table 1). There was no significant interaction between efficacy and the quartile of center-based TTR (p interaction=0.29). Similarly, the primary safety endpoint of ISTH major bleeding was reduced in each center-based TTR stratum with apixaban compared with warfarin, with a trend toward greater reduction at centers with lower TTRs but with no statistically significant interaction (p interaction=0.10; Table 2). The secondary safety endpoint of major or clinically relevant minor bleeding was also reduced with apixaban, with a more robust reduction at centers with lower TTRs and significant interaction (p interaction=0.005; Table 2).

Table 1. SSE in Relation to Centers' TTRs.

	Apixaban		Warfarin			
Center TTR (%)	Events	Rate/100 person years	Events	Rate/100 person years	HR (95% CI)	Adjusted Interaction
<58.0	70	1.75	88	2.28	0.77 (0.56 to 1.06)	0.29
58.0 to 65.7	54	1.30	68	1.61	0.80 (0.56 to 1.15)	
65.7 to 72.2	51	1.21	65	1.55	0.79 (0.54 to 1.13)	
>72.2	36	0.83	44	1.02	0.81 (0.52 to 1.26)	

TTR=Time-therapeutic range; HR = Hazard ratio; CI = Confidence interval

There were consistent reductions in mortality and the composite efficacy endpoint of SSE and myocardial infarction with apixaban in each stratum, with no