Electrophysiology

Apixaban versus warfarin in patients with atrial fibrillation according to prior warfarin use: Results from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial

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Background Patients with atrial fibrillation who are vitamin K antagonist (VKA)-naive may have a higher risk of thrombosis and/or bleeding than VKA-experienced patients.

Methods and results Using data from ARISTOTLE, we assessed baseline characteristics and the treatment effect of apixaban versus warfarin in the VKA-naive and VKA-experienced cohorts. We compared rates of study drug discontinuation and time-in-therapeutic range. Overall, 7,800 (43%) were VKA naive, and 10,401 were VKA experienced. At baseline, both groups were similar with respect to age and congestive heart failure, hypertension, age, diabetes, stroke score ($CHADS_2$). Fewer VKA-naive patients had a history of prior stroke (18% vs 21%) or prior bleeding (10% vs 22%) and were more often female (39% vs 33%). The effect of apixaban on the primary efficacy and safety outcomes was similar in VKA-naive (stroke/systemic embolism: hazard ratio [HR] 0.86, 95% CI 0.67-1.11 and major bleeding: HR 0.73, 95% CI 0.59-0.91) and VKA-experienced populations (stroke/systemic embolism: HR 0.73, 95% CI 0.57-0.95, *P* value for interaction = 0.39 and major bleeding: HR 0.66, 95% CI 0.55-0.80, *P* value for interaction = 0.50). Permanent study drug discontinuation was numerically less likely in patients receiving apixaban whether they were VKA naive (HR for discontinuation: 0.87, 95% CI 0.79-0.95) or VKA experienced (HR for discontinuation: 0.93, 95% CI 0.85-1.02). Among patients receiving warfarin, the mean/median times in therapeutic range were lower in the VKA-naive group (VKA-naive: 57.5/61.4, VKA-experienced: 66.0/69.1, $P < .001$).

Conclusion The treatment effects of apixaban (vs warfarin) were not modified by VKA naivety. The rates of stroke/systemic embolism and major bleeding were numerically lower among the patients assigned to apixaban, irrespective of prior VKA use. (Am Heart J 2013;166:549-58.)

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Vitamin K antagonists (VKAs), along with newer oral anticoagulants such as dabigatran, rivaroxaban, or apixaban, reduce the risk of stroke in patients with atrial fibrillation (AF). However, retrospective observations suggest that patients with little or no prior exposure to anticoagulation (ie, VKA naive) may be at higher risk for adverse outcomes (thromboembolic events and/or bleeding) than patients who are VKA experienced.[1] In a meta-analysis of 29 randomized controlled trials and 4 prospective cohort studies, 1.48% of VKA-treated patients had intracranial hemorrhage (ICH) in the first 3 months of treatment, whereas after the first 3 months of exposure, the rate of intracranial bleeding was 0.65 per 100 patient-years.[2] In a post hoc analysis of the ACTIVE-W trial randomizing patients with AF to receive a VKA or clopidogrel plus aspirin, the advantage of VKA treatment was less pronounced in the 1,553 patients (23%) who

Table I. Baseline characteristics: VKA-naive and VKA-experienced subjects

Characteristic	VKA naive			VKA experienced			P*
	Overall (n = 7800)	Apixaban (n = 3912)	Warfarin (n = 3888)	Overall (n = 10,401)	Apixaban (n = 5208)	Warfarin (n = 5193)	
Age, median (25th, 75th), y	70 (62, 76)	70 (62, 76)	70 (62, 76)	70 (63, 76)	70 (64, 76)	70 (63, 76)	<.0001
Female sex, n (%)	3039 (39.0)	1514 (38.7)	1525 (39.2)	3377 (32.5)	1720 (33.0)	1657 (31.9)	<.0001
Region, n (%)							<.0001
North America	1127 (14.4)	554 (14.2)	573 (14.7)	3347 (32.2)	1695 (32.5)	1652 (31.8)	
Latin America	1589 (20.4)	789 (20.2)	800 (20.6)	1879 (18.1)	954 (18.3)	925 (17.8)	
Europe	3524 (45.2)	1791 (45.8)	1733 (44.6)	3819 (36.7)	1881 (36.1)	1938 (37.3)	
Asia Pacific	1560 (20.0)	778 (19.9)	782 (20.1)	1356 (13.0)	678 (13.0)	678 (13.1)	
Systolic BP, median (25th, 75th), mm Hg	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)	<.0001
Weight, median (25th, 75th), kg	80 (68, 93)	80 (68, 93)	80 (68, 93)	84 (72, 98)	84 (71, 98)	84 (72, 98)	<.0001
Prior MI, n (%)	1045 (13.4)	541 (13.8)	504 (13.0)	1540 (14.8)	778 (14.9)	762 (14.7)	.0072
Prior clinically relevant or spontaneous bleeding, n (%)	788 (10.1)	402 (10.3)	386 (9.9)	2252 (21.7)	1123 (21.6)	1129 (21.7)	<.0001
History of fall within previous year, n (%)	240 (3.4)	116 (3.3)	124 (3.6)	513 (5.4)	270 (5.7)	243 (5.1)	<.0001
Type of AF, n (%)							<.0001
Paroxysmal	1334 (17.1)	660 (16.9)	674 (17.3)	1452 (14.0)	714 (13.7)	738 (14.2)	
Persistent or permanent	6465 (82.9)	3251 (83.1)	3214 (82.7)	8947 (86.0)	4493 (86.3)	4454 (85.8)	
Qualifying risk factors, n (%)							
Age ≥75 y	2288 (29.3)	1145 (29.3)	1143 (29.4)	3390 (32.6)	1705 (32.7)	1685 (32.4)	<.0001
Prior stroke, TIA, or systemic embolism	1385 (17.8)	690 (17.6)	695 (17.9)	2153 (20.7)	1058 (20.3)	1095 (21.1)	<.0001
HF or reduced LVEF	3087 (39.6)	1553 (39.7)	1534 (39.5)	3364 (32.3)	1682 (32.3)	1682 (32.4)	<.0001
Diabetes	1830 (23.5)	920 (23.5)	910 (23.4)	2717 (26.1)	1364 (26.2)	1353 (26.1)	<.0001
Hypertension requiring treatment	6898 (88.4)	3446 (88.1)	3452 (88.8)	9018 (86.7)	4516 (86.7)	4502 (86.7)	.0005
$CHADS_2$, mean (SD)	2.1 (1.1)	2.1 (1.1)	2.1 (1.1)	2.1 (1.1)	2.1 (1.1)	2.1 (1.1)	.7519
$CHADS_2$ score							.0076
≤1	2589 (33.2)	1295 (33.1)	1294 (33.3)	3594 (34.6)	1805 (34.7)	1789 (34.5)	
2	2892 (37.1)	1457 (37.2)	1435 (36.9)	3624 (34.8)	1805 (34.7)	1819 (35.0)	
≥3	2319 (29.7)	1160 (29.7)	1159 (29.8)	3183 (30.6)	1598 (30.7)	1585 (30.5)	
Medications at baseline, n (%)							
Aspirin	3455 (44.3)	1780 (45.5)	1675 (43.1)	2177 (20.9)	1079 (20.7)	1098 (21.1)	<.0001
Clopidogrel	193 (2.5)	98 (2.5)	95 (2.4)	145 (1.4)	72 (1.4)	73 (1.4)	<.0001
Statin	2622 (34.3)	1324 (34.7)	1298 (34.0)	4851 (47.2)	2426 (47.2)	2425 (47.3)	<.0001
NSAIDs	481 (6.3)	226 (5.9)	255 (6.7)	1039 (10.1)	526 (10.2)	513 (10.0)	<.0001

BP, Blood pressure; *HF*, heart failure; *LVEF*, left ventricular ejection fraction; *NSAID*, nonsteroidal anti-inflammatory drug; *TIA*, transient ischemic attack.
* *P* value corresponds to comparison of VKA naive versus VKA experienced for each characteristic.

were retrospectively observed not to be on oral anticoagulation at study entry (relative risk for stroke, myocardial infarction [MI], vascular death, or major bleeding 0.91) than in the 5,153 patients who were on oral anticoagulation at baseline (relative risk for stroke, MI, vascular death, or major bleeding 0.66).[3] In contrast, in the RE-LY trial of patients with AF, the randomization to dabigatran or warfarin was stratified for VKA naivety, and each center had to recruit at least 50% VKA-naive patients. With this design, the relative effects of dabigatran (vs warfarin) on the primary end points did not differ according to prior VKA experience; permanent and premature discontinuation of study drug was the only outcome that was consistently more common among VKA-naive patients.[4]

The ARISTOTLE trial demonstrated that a new oral factor Xa inhibitor, apixaban, had better safety and better efficacy than warfarin in patients with AF.[5] In the present analysis, we aimed to evaluate whether the treatment effects of apixaban compared with warfarin were different for patients who were VKA naive compared with those who were VKA experienced.

Methods

ARISTOTLE trial

ARISTOTLE was a double-blind study in which 18,201 patients with AF from 1,034 clinical centers were randomly assigned to either receive warfarin (target international normalized ratio [INR] 2-3) or apixaban 5.0 mg by mouth twice daily.