Apixaban Superior to Warfarin in Patients with Atrial Fibrillation as well as Prior Stroke or TIA

Written by Rita Buckley

The recent Apixaban Compared with Warfarin in Patients with Atrial Fibrillation and Prior Stroke or Transient Ischemic Attack trial [Granger CB et al. *N Engl J Med* 2011; ARISTOTLE; NCT00412984] found apixaban to be superior to warfarin for stroke prevention in a wide range of atrial fibrillation (AF) patients, with significantly lower bleeding risk and lower risk of all-cause mortality [Littrell R, Flaker G. *Expert Rev Cardiovasc Ther* 2012]. J. Donald Easton, MD, FAHA, University of California, San Francisco, California, USA, presented results of a comparison of apixaban with warfarin in patients with AF and prior stroke or transient ischemic attack (TIA).

ARISTOTLE was a randomized, double-blind, double-dummy trial that included subjects who were aged ≥75 years and had AF and at least one additional risk factor for stroke (previous stroke, TIA, or systemic embolism [SE]; symptomatic heart failure within the previous 3 months or left ventricular ejection fraction ≤40%; diabetes mellitus; or hypertension requiring pharmacologic treatment). A total of 18,201 patients were randomized to apixaban 5 mg oral BID or warfarin (target INR 2 to 3). The primary outcome was ischemic or hemorrhagic stroke or SE. The trial was designed to test for noninferiority, with key secondary objectives of testing for superiority with respect to the primary outcome and to the rates of major bleeding and death from any cause.

The primary objective of the stroke substudy was to determine whether apixaban, as compared with warfarin, had the same advantages in patients with prior stroke or TIA (n=3436) as in all patients (n=14,765) with AF in the ARISTOTLE trial. The primary efficacy outcome was ischemic or hemorrhagic stroke or SE. The primary safety outcome was major bleeding according to the International Society of Thrombosis and Hemostasis (ISTH) definition.

The demographic and clinical characteristics of the Prior Stroke/TIA patients compared with the No Prior Stroke/TIA patients were essentially the same, with 19.5% of the 18,201 ARISTOTLE patients having had a prior stroke or TIA. The only important difference was in the $CHADS_2$ score (mean, SD): 3.7 (0.9) for the Prior Stroke/TIA group versus 1.7 (0.8) for the No Prior Stroke/TIA group. Only 15% of the No Prior Stroke/TIA group had a $CHADS_2$ score that high.

The primary outcome data (Figure 1) showed a considerably higher event rate in the warfarin/Prior Stroke group compared with the apixaban/Prior Stroke group, indicating a greater absolute benefit in the apixaban group. In the hazard ratio outcomes, all p values were nonsignificant, demonstrating comparable benefit in the Prior Stroke/TIA and No Prior Stroke/TIA groups. Efficacy outcomes also had nonsignificant interaction p values, indicating a consistent benefit between the two groups (Table 1). The safety outcomes showed that the benefit always accrued to apixaban. Nonsignificant interaction p values indicated that the results in both groups were equally beneficial.

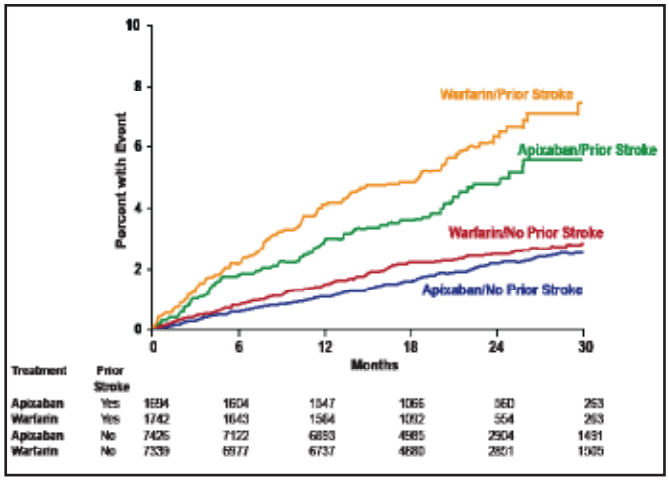
Summary data showed that treatment with apixaban compared with warfarin in patients with AF and prior stroke or TIA reduced stroke and SE by 24%, major bleeding by 27%, intracranial bleeding by 63%, and mortality by 11%.

Table 1. Stroke Substudy Efficacy Outcomes.

	Prior Stroke or TIA			No Prior Stroke or TIA			p value (interaction)
	Apixaban	Warfarin	HR (95% CI)	Apixaban	Warfarin	HR (95% CI)	
	n (Rate*)	n (Rate*)	Apixaban vs Warfarin	n (Rate*)	n (Rate*)	Apixaban vs Warfarin	
Primary Efficacy Outcome (Stroke or Systemic Embolism)	73 (2.46)	98 (3.24)	0.76 (0.56-1.03)	139 (1.01)	167 (1.23)	0.82 (0.65-1.03)	0.71
Stroke	67 (2.26)	96 (3.17)	0.71 (0.52-0.98)	132 (0.96)	154 (1.14)	0.84 (0.67-1.06)	0.40
Hemorrhagic	12 (0.40)	31 (1.00)	0.40 (0.21-0.78)	28 (0.20)	47 (0.34)	0.59 (0.37-0.94)	0.35
Ischemic or uncertain	57 (1.92)	68 (2.23)	0.86 (0.60-1.22)	105 (0.76)	107 (0.79)	0.97 (0.74-1.26)	0.61
Disabling or fatal	39 (1.31)	46 (1.49)	0.87 (0.57-1.34)	46 (0.33)	76 (0.56)	0.60 (0.41-0.86)	0.18
Myocardial infarction	17 (0.57)	28 (0.91)	0.62 (0.34-1.14)	73 (0.53)	74 (0.54)	0.97 (0.70-1.34)	0.20
Cardiovascular death	72 (2.35)	76 (2.41)	0.98 (0.71-1.35)	236 (1.68)	268 (1.94)	0.87 (0.73-1.03)	0.53
Death from any cause	129 (4.22)	150 (4.77)	0.89 (0.70-1.12)	474 (3.37)	519 (3.75)	0.90 (0.79-1.02)	0.89

*Rate per 100 patient/years of follow-up; Reproduced with permission from JD Easton, MD.

Figure 1. Stroke Substudy Primary Outcome.



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Overall, the trial demonstrated that in patients with AF and prior stroke or TIA, apixaban is superior to warfarin in preventing stroke or SE; causes less bleeding, especially intracranial bleeding; and results in lower mortality. These outcomes are consistent with those of the main ARISTOTLE trial.

No Compelling Evidence to Use Warfarin or Aspirin in HF Patients

Written by Rita Buckley

The Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction Trial [WARCEF; NCT00041938] found no compelling evidence to use warfarin for all patients. Shunichi Homma, MD, Columbia University College of Physicians and Surgeons, New York, New York, USA, reported outcomes from the study.

WARCEF was a randomized, double-blind, multicenter, international clinical trial. The primary outcome was to determine if warfarin or aspirin was superior for preventing the combined endpoint of death, ischemic stroke, or intracerebral hemorrhage (ICH) in patients with left ventricular ejection fraction (LVEF) ≤35% in sinus rhythm. The mean follow-up was 3.5 years, ranging from 1 to 6 years.

The main secondary aim was to determine if warfarin or aspirin was superior for preventing death, ischemic stroke, or ICH plus myocardial infarction or heart failure (HF) hospitalization in patients with LVEF ≤35% in sinus rhythm.

A total of 2305 patients were randomized to receive either warfarin (target INR 2 to 3.5; n=1142) or 325 mg/day of aspirin (n=1163). Key inclusion criteria included normal sinus rhythm, LVEF ≤35%, no defined cardioembolic source, and being on an optimal HF regimen.

Baseline characteristics were similar between the two groups, as was baseline time in the therapeutic range (63%; 2 to 3.5). The mean INR was 2.5±0.95. The number of patient-years in the aspirin group was 4033; in the warfarin group, the number of patient years was 4045. The primary analysis was treatment-by-time interaction.

The combined primary outcome was not significantly different between groups, occurring at a rate of 7.47% per year among warfarin patients versus 7.93% per year in those who were assigned to aspirin (HR, 0.93; 0.79 to 1.10; p=0.40; Figure 1). There was, however, a suggestive benefit of warfarin for the primary outcome at 4 years and beyond (HR, 0.894; 0.800 to 0.998; p=0.046; Figure 2).

Figure 1. Primary Outcome.

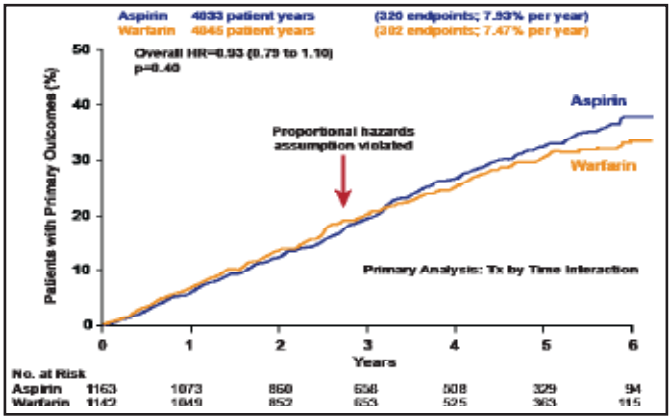

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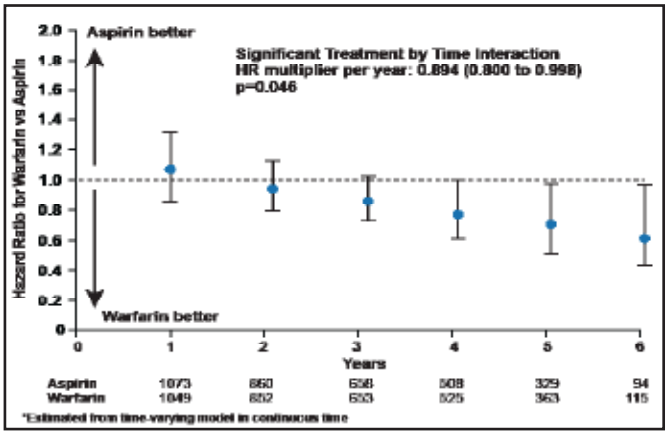
Figure 2. Warfarin vs Aspirin Hazard Ratios by Year of Follow-Up (Prespecified Time-Varying Analysis).



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The warfarin group (n=268) had a death rate of 6.63% per year. The death rate in the aspirin group (n=263) was 6.52% per year (HR, 1.01; 95% CI, 0.85 to 1.21; p=0.91).