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ATRIAL FIBRILLATION

ARISTOTLE reveals superiority of apixaban over warfarin in patients with atrial fibrillation

The eagerly awaited findings of the ARISTOTLE trial were presented at the 2011 European Society of Cardiology Congress in Paris, France, and simultaneously published online in the *New England Journal of Medicine* on Sunday 28 August. Apixaban was not only found to be noninferior to warfarin in the prevention of stroke or systemic embolism in patients with atrial fibrillation (AF) and at least one other risk factor for stroke, but was actually shown to be superior to this 'gold standard' antithrombotic treatment, owing to a reduction in risk of hemorrhagic stroke, bleeding, and all-cause death.

Although very effective at preventing stroke in patients with AF, warfarin is notoriously difficult to use, owing to its narrow therapeutic range and the associated need for regular monitoring and dose adjustment, as well as the known drug and food interactions and the increased risk of bleeding that are associated with this drug. As a result, there is a great need for more-straightforward and convenient anticoagulation therapies.

Apixaban is a direct oral factor Xa inhibitor of interest to clinicians because of its ease of use, rapid absorption, and 12 h half-life. Encouragingly, as the ARISTOTLE investigators point out in their trial report, compared with low-dose aspirin for stroke prevention in patients with AF, apixaban "was shown to substantially reduce the risk of stroke without any difference in the rates of major bleeding and with lower rates of discontinuation [in the AVERROES trial]." In a large, double-blind, randomized, controlled, phase III study, the ARISTOTLE investigators set out to compare apixaban with warfarin, the current 'gold standard' antithrombotic therapy for patients with AF. As AF expert Professor Gregory Lip, from City Hospital in Birmingham, UK, points out, "such a trial would be needed for registration [of apixaban] in this indication."

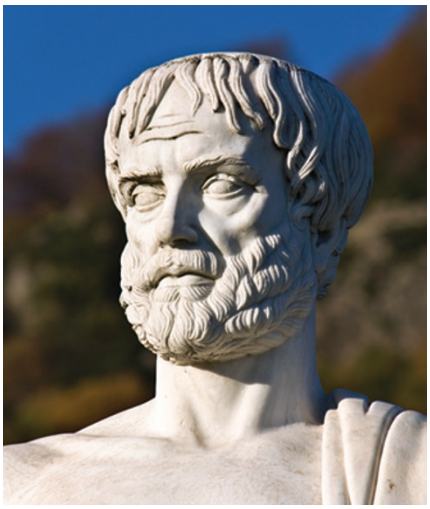
In total, 18,201 patients were enrolled at 1,034 clinical sites in 39 countries between December 2006 and April 2010. Of the patients assigned to receive apixaban ($n = 9{,}120$) or warfarin ($n = 9{,}081$), 15% had paroxysmal AF and 85% had persistent or permanent forms of the disorder. All enrolled patients had at least one other risk factor for stroke, such as age ≥75 years, hypertension requiring pharmacological treatment, symptomatic heart failure within the previous 3 months, or previous stroke, transient ischemic attack, or systemic embolism. Compared with the warfarin group, fewer patients assigned to receive apixaban discontinued the study drug during follow-up (25.3% vs 27.5%, $P = 0.001$).

The primary efficacy outcome of the trial—stroke or systemic embolism—occurred in fewer patients assigned to apixaban as opposed to warfarin (HR 0.79, 95% CI 0.66–0.95, $P < 0.001$ for noninferiority and $P = 0.01$ for superiority of apixaban). This apixaban-associated reduction in the primary efficacy outcome was consistent across all major subgroups.

The apparent better efficacy of apixaban over warfarin resulted from a lower rate of hemorrhagic stroke with the oral factor Xa inhibitor (HR 0.51, 95% CI 0.35–0.75, $P < 0.001$); neither rates of ischemic or uncertain type of stroke (HR 0.92, 95% CI 0.74–1.13, $P = 0.42$) nor rates of systemic embolism (HR 0.87, 95% CI 0.44–1.75, $P = 0.70$) were significantly different between the two treatment arms.

The key secondary efficacy outcome—death from any cause—was also reduced in the apixaban group (HR 0.89, 95% CI 0.80–0.998, $P = 0.047$).

ISTH major bleeding, the primary safety outcome of the trial, was significantly lower in the apixaban group than in the warfarin group (HR 0.69, 95% CI 0.60–0.80, $P < 0.001$). This finding was consistent across all major subgroups except when presence of diabetes mellitus or level of renal impairment was considered; greater reductions were found in individuals who did not have diabetes compared with patients with the disease, and in participants with moderate to severe renal impairment as opposed to mild or no impairment.



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All other assessed classifications of bleeding, including GUSTO severe bleeding, GUSTO moderate or severe bleeding, TIMI major bleeding, TIMI major or minor bleeding, and any bleeding, were also substantially lower in the apixaban group. Rates of all adverse events (81.5% vs 83.1% for the apixaban and warfarin groups, respectively), and for serious adverse events (35.0% vs 36.5%, respectively), were comparable for the apixaban and warfarin groups.

After the publication of what Gregory Lip describes as "very compelling and impressive data", the reactions of regulatory authorities and, subsequently, prescribing clinicians will be of great interest. Will apixaban soon become a common choice of anticoagulant for patients with AF?

Bryony M. Mearns

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