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Pfizer and Bristol's ARISTOTLE Study Finds the Golden Mean of Anticoagulation

In ancient Greece the philosopher Aristotle thought the golden mean was the desirable middle between two extremes, one of excess and the other of deficiency. In cardiology, apixaban may be the golden mean of anticoagulation, achieving the ideal balance of reduced strokes and deaths without causing any additional bleeding complications.

Chris Granger and Lars Wallentin at the ESC Press Conference

The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study compared warfarin to apixaban (5 mg twice daily) in 18,201 patients with AF and at least one additional risk factor for stroke. The overachieving trial demonstrated that apixaban (Eliquis, Pfizer and Bristol-Myers Squibb) was not only noninferior to warfarin in efficacy, it was superior. Further, treatment with apixaban resulted in a statistically significant reduction in mortality, and reduced the risk of major bleeding. The results of ARISTOTLE were presented by Christopher Granger on Sunday morning at the European Society of Cardiology meeting in Paris and published simultaneously in the *New England Journal of Medicine*.

Here are the key details:

After 1.8 years of followup, **stroke or systemic embolism** (the primary endpoint) occurred in 212 out of 9120 apixaban-treated patients versus 265 out of 9081 warfarin-treated patients:

- Yearly rate: 1.27% in the apixaban group versus 1.60% in the warfarin group (HR 0.79, CI 0.66-0.95, p<0.001 for noninferiority, p=0.01 for superiority)

Major bleeding occurred in 327 of the apixaban-treated patients versus 462 of the warfarin-treated patients.

- Yearly rate: 2.13% versus 3.09% (HR 0.69, CI 0.60-0.80, p<0.001

Death occurred in 603 apixaban-treated patients versus 669 warfarin-treated patients.

- Yearly rate: 3.52% versus 3.94% (HR 0.89, CI 0.80-0.99, p=0.047)
- Yearly rate of death from cardiovascular causes: 1.80% versus 2.02% (HR 0.89, CI 0.76-1.04)

Hemorrhagic stroke occurred in 40 apixaban-treated patients versus 78 warfarin-treated patients.

- Yearly rate: 0.24% versus 0.47% per year (HR 0.51, CI 0.35-0.75, p<0.001)

Ischemic or uncertain stroke occurred in 162 apixaban-treated patients versus 175 warfarin-treated patients.

- Yearly rate: 0.97% per year vs 1.05%, HR 0.92, CI 0.74-1.13, p=0.42)

Stroke, systemic embolism, MI, or death from any cause occurred in 810 apixaban-treated patients versus 906 warfarin-treated patients.

- Yearly rate: 4.85% versus 5.49%, HR 0.88, p=0.01

The results were consistent across a broad range of subgroups. Of note, there were no significant differences between geographic regions. There was a greater reduction in major bleeding associated with apixaban in nondiabetics compared to diabetics (p=0.003 for interaction) and in patients with moderate or severe renal impairment compared to those with mild or no renal impairment ((p=0.03 for interaction).

The investigators calculated that for every 1000 patients treated with apixaban instead of warfarin for 1.8 years

- stroke would be avoided in 6 patients,
- major bleeding would be avoided in 15 patients, and
- death would be avoided in 8 patients.

Comparing their results with the RE-LY trial of dabigatran, the authors wrote that apixaban "appears to combine the advantages of each of the two doses of dabigatran, with both a greater overall reduction in the rate of stroke and a lower rate of bleeding than the rates with warfarin." They also noted that in the ROCKET AF trial rivaroxaban lowered intracranial hemorrahge and fatal bleeding but was not better than warfarin in other major bleeding. They listed possible reasons for the differences in trials of the three drugs: "differences in the doses of drugs, the pharmacokinetic and pharmacodynamic properties of the drugs, patient populations, or other features of the clinical-trial design."

They also noted that the 3 novel anticoagulants (apixaban, dabigatran, and rivaroxaban) have all demonstrated a lower risk of hemorrhagic stroke compared to warfarin, suggesting "a specfic risk associated with warfarin, possibly related to its inhibition of multiple coagulation factors or interaction between warfarin and tissue factor VIIa complexes in the brain."

In an accompanying editorial, Jessica Mega called the ARISTOTLE results "impressive" and wrote that "a new era of anticoagulation in patients with atrial fibrillation appears to be emerging." She said that all three newer anticoagulants significantly reduce hemorrhagic stroke and have similar effects on mortality, though the difference in mortality was significant only in ARISTOTLE. The three drugs, she writes, "have been shown to have a more favorable bleeding profile than warfarin and are at least as efficacious."

In an interview, Christopher Granger, the first author of the study, said that the investigators felt "as though we hit the sweet spot" with the drug in the trial, achieving greater efficacy in preventing stroke while also producing a "really remarkable reduction in major bleeding, and all with a drug that's really very well tolerated" and that has produced "no real safety signal."

In addition, Granger said that the results in the United States appear to be consistent with the overall trial, although a detailed analysis has not yet been performed.

Granger speculated that after the forthcoming ENGAGE AF=TIMI 48 trial with edoxaban, "there will not be another large trial with a a warfarin comparator."

At the ESC press conference for ARISTOTLE, Lars Wallentin presented results of the trial stratified by the time in the therapeutic range (TTR). Although the benefits of apixaban were more pronounced in centers with poor INR control, apixaban was still beneficial in centers that had good INR control.

Click here to download the press release from Bristol-Myers Squibb and Pfizer: 082811 ARISTOTLE ESC Data Release copy

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