

P4752

**Apixaban 2.5 mg twice daily is effective and safe for patients with atrial fibrillation and combinations of advanced age, low body weight, and elevated creatinine: insights from ARISTOTLE**

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**Background:** In ARISTOTLE, patients with atrial fibrillation and  $\geq 2$  dose-reduction criteria [age  $\geq 80$  years, weight  $\leq 60$  kg, and creatinine  $\geq 1.5$  mg/dL (133  $\mu$ mol/L)] were randomized to apixaban 2.5 mg twice daily (b.i.d) or warfarin.

**Purpose:** To determine whether the apixaban dose adjustment in ARISTOTLE resulted in similar efficacy and safety compared to warfarin.

**Methods:** The effects of apixaban 2.5 mg b.i.d versus warfarin on stroke or systemic embolism, major bleeding and death in ARISTOTLE patients with  $\geq 2$  dose-reduction criteria were compared with the effects of apixaban 5 mg b.i.d in patients with 0 or 1 dose-reduction criterion.

**Results:** Of 751 (4.1%) patients with  $\geq 2$  dose-reduction criteria, 386 were assigned to apixaban 2.5 mg b.i.d and 365 to warfarin. Compared to patients with 0 or 1 dose reduction criteria (n=17,322), these patients had a

higher risks of stroke/systemic embolism (HR =1.78; 95% CI [1.24–2.57]), major bleeding (HR =1.73; 95% CI [1.28–2.32]) and death (HR=3.21; 95% CI [2.69–3.83]), irrespective of whether they were assigned to apixaban or warfarin. The benefits of apixaban 2.5 mg b.i.d compared with warfarin on stroke or systemic embolism, major bleeding, and death in patients with  $\geq 2$  dose-reduction criteria were consistent with that of apixaban 5 mg b.i.d in patients with either 0 or 1 dose-reduction criteria (Figure).

**Conclusions:** While they are at higher overall risk, patients with appropriate dose reduction criteria have consistent benefits with apixaban 2.5 mg b.i.d. over warfarin. Additional analyses investigating the relationship between apixaban dose and both apixaban plasma concentrations and levels of thrombosis biomarkers are underway.

Risk of events and effect of apixaban versus warfarin according to dose-reduction criteria

