For stroke prevention in atrial fibrillation (AF), warfarin has been the king of the castle for more than half a century. Recently, some serious contenders have threatened its dominance by claiming therapeutic equivalence and a better benefit–risk profile. These novel agents, oral direct thrombin or factor Xa inhibitors, have kindled anticipation of “a new era for anticoagulation in AF.”

On August 28, 2011, the New England Journal of Medicine published online the primary results of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial (ARISTOTLE; ClinicalTrials.gov number NCT00412984). The study demonstrated convincing evidence of the benefits of the direct factor Xa inhibitor apixaban (Eliquis; Pfizer/Bristol-Myers Squibb) over warfarin in patients with AF. Before apixaban, 2 other novel anticoagulants, dabigatran and rivaroxaban, made it through phase III trials and were subsequently approved by the Food and Drug Administration. Apixaban, however, was the first new anticoagulant to achieve its dominance by claiming therapeutic equivalence and a better benefit–risk profile. They are immediately active in their functional role after coagulation checks and may offer improved benefit-to-risk profile. Hence, they can be administered at fixed doses without routine coagulation checks and may offer improved benefit-to-risk profile. They are immediately active in their functional role after being absorbed from the gut. In the case of bleeding, their shorter half-lives make management easier because of faster elimination from the plasma. Nevertheless, promises of convenient use and improved safety are not likely to gain quick favor among patients and physicians who may be reluctant to change a winning horse.

Which Promises Has ARISTOTLE Kept?
ARISTOTLE has kept virtually all of its promises. ARISTOTLE was a randomized, double blind, double-dummy trial that compared apixaban (5 mg twice daily) with warfarin (to a target international normalized ratio of 2–3) in 18 201 patients with AF and at least 1 additional risk factor for stroke. The mean CHADS2 score for the study population was 2.1. The primary efficacy outcome was the composite of stroke and systemic embolism; the primary safety outcome was major bleeding.

Comparisons of the primary outcomes and of all-cause death were analyzed as part of hierarchical sequence testing, starting with testing the primary efficacy outcome for noninferiority (upper limit of 95% CI <1.38 and upper limit of 99% CI <1.44), then the primary efficacy outcome for superiority, then major bleeding, and, finally, all-cause death. The efficacy analyses included all randomized patients (“intention to treat”); bleeding analyses were “on treatment” and included all randomized patients who received at least 1 dose of study drug.

Apixaban demonstrated noninferiority for the primary efficacy outcome compared with warfarin (P<0.001). The annual event rates (stroke or systemic embolism) were 1.27% on apixaban and 1.60% on warfarin. The secondary key objectives were also met: apixaban was superior to warfarin for the primary efficacy outcome (P=0.01), the primary safety outcome (P<0.001), and all-cause mortality (P=0.047). The relative risk reduction with apixaban was 21% for stroke or systemic embolism (49% for hemorrhagic stroke and 8% for ischemic stroke), 31% for major bleeding (56% for intracranial hemorrhage), and 11% for all-cause death. Compared with warfarin, apixaban prevented 4 hemorrhagic strokes, 2 ischemic or uncertain types of strokes, 15 major bleeds, and 8 deaths per 1000 patients treated over 1.8 years. Safety and efficacy findings were consistent across subgroups, including geographic regions, age, sex, previous warfarin experience, and differences in renal function as well as in other predefined subgroups. There were no

Critique of Apixaban Versus Warfarin in Patients With Atrial Fibrillation

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Inferiors revolt in order that they may be equal, and equals that they may be superior. Such is the state of mind, which creates revolutions.
—Aristotle. In: Politics. Book V; Part II; 350 B.C.E.
unexpected side effects, and the rate of the study drug discontinuation was lower in the apixaban group than in the warfarin group.

What Are the Methodological Strengths of ARISTOTLE?
ARISTOTLE addressed relevant clinical outcomes. It included equal proportions of patients at low, moderate, and high risk for stroke; hence, comparisons between apixaban and warfarin apply to a broad spectrum of AF patients. Warfarin was within the therapeutic range 66% of the study time, which is similar to the corresponding time in RE-LY (64%) and longer than the time in ROCKET-AF (55%). The benefits of apixaban were consistent irrespective of how well warfarin was used at different centers, as measured by the time in therapeutic range. The large sample size allowed for important insights into the effect of apixaban across predefined subgroups, and there were no significant subgroup interactions for the primary efficacy outcome. For the primary safety outcome, apixaban produced a greater reduction of major bleeding in patients who did not have diabetes mellitus \( (P = 0.003) \) and among those with moderate or severe renal impairment \( (P = 0.03) \).

Is There a Flip Side to the Coin?
Along with numerous strengths, there were some limitations. First, the observation period of 1.8 years did not provide information on the long-term effects of apixaban in patients with AF. However, the benefits of apixaban remained consistent over the study period so that “wearing off” in the long-term is not likely. Second, the drug is not yet studied in patients with severe renal insufficiency (serum creatinine level of >221 \( \mu \)mol/L or calculated creatinine clearance of <25 mL per minute). Although only \( \approx 25\% \) of apixaban is eliminated through the kidneys, severely impaired renal function might lead to retention of the drug and an increase of the bleeding risk. Third, little is known about possible interactions with concomitant medication. Potent inhibitors of CYP3A4 such as azole antifungals or protease inhibitors can slow the hepatic metabolism of apixaban. However, in vitro studies have demonstrated that metabolic interactions between apixaban and coadministered drugs are unlikely because of multiple clearance pathways.

The Battle for Market Share
In ARISTOTLE, apixaban appeared not just “noninferior” but “superior” to warfarin in the 3 major outcomes. Showing superiority versus warfarin is going to be a key to its successful marketing and widespread use. The 1 issue that might slow down the take-off of apixaban is cost. In analogy to recent economic analyses with dabigatran, apixaban is likely to be particularly cost-effective in patients at increased risk for stroke or in whom the international normalized ratio is likely to be less well-controlled. Switching to a new agent may not be necessary for patients in whom the international normalized ratio has been well-controlled with warfarin.

Concerning the new anticoagulation agents, important questions remain regarding their respective efficacy and safety profiles, particularly as they compare to one another. There are no head-to-head trials comparing apixaban with other novel anticoagulants. Indirect comparisons appear to be favoring apixaban at the current time.

Unlike dabigatran, which was recently linked to 256 deaths from bleeding across the world, there were no safety issues with apixaban in patients with moderate to severe renal impairment (patients with serum creatinine level of >221 \( \mu \)mol/L were not included in the ARISTOTLE study). Also, the concerns about possible increase in myocardial infarction rate with dabigatran versus warfarin in RE-LY were not substantiated in ARISTOTLE. However, apixaban did not show a reduction in ischemic stroke as was seen with the 150 mg dabigatran dose in RE-LY.

Rivaroxaban was shown to be noninferior to warfarin in preventing stroke. Superiority, however, was demonstrated in the “as-treated” but not in the “intention-to-treat” analysis. Rivaroxaban does have the advantage of once-daily dosing regimen that is considered important for patient compliance.

Conclusions
We are witnessing the uprising of novel anticoagulants that seek to overthrow the hegemony of warfarin in patients with AF. The results of ARISTOTLE have positioned apixaban as the most promising new agent, a true successor to the throne, achieving reductions in each of the major outcomes of stroke, bleeding, and mortality. The king has not been crowned yet, and before true ascendance to the throne can be achieved, phase IV studies are needed to show a long-term optimal balance between efficacy and safety.

Disclosures
Dr Nedeltchev is a member of the advisory board of Boehringer Ingelheim (Schweiz) GmbH and Bayer (Schweiz) AG.

References

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