# Landmark Trials: Newer Anticoagulants in Atrial Fibrillation – Heralding Hope!

Rahul Mehrotra, MD, DNB, Manish Bansal, MD, DNB, Ravi R. Kasliwal, MD, DM, *Gurgaon, India.*

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice and the prevalence has been steadily increasing. Stroke and systemic embolism are the gravest complications of this disorder with the risk being as high as seven times the general population in patients with additional risk factors. For the past 50 years, vitamin-K antagonists like warfarin have been the most effective agents for prophylaxis of stroke and systemic embolism in patients with AF. Although their efficacy has been unmatched and they have been shown to be superior to antiplatelet therapy, the need of regular prothrombin time (PT-INR) monitoring, numerous interactions with drugs and food, failure to achieve the desired international normalized ratio (INR) value despite regular drug intake, the risk of bleeding, and teratogenicity are few reasons why the compliance rates with these drugs have consistently been suboptimal (to the tune of 50–60%). Thus, physicians and patients both have been on the lookout for better options. Three new orally active drugs (dabigatran, apixaban, and rivaroxaban), acting by direct thrombin inhibition or by exhibiting anti factor-Xa activity, have been evaluated in three large clinical trials (RE-LY, ARISTOTLE, and ROCKET-AF) in patients with nonvalvular AF. All these drugs, given in a fixed dose, do not require PT-INR monitoring. The excellent efficacy and safety demonstrated by these drugs, along with the ease of use, has generated lot of interest among cardiologists and neurologists and has led to their approval too. We thus considered it pertinent to discuss these landmark trials that promise to be "game changers" in the management of AF.

From: Medanta-The Medicity, Gurgaon, India (R.M., N.B., R.R.K.)

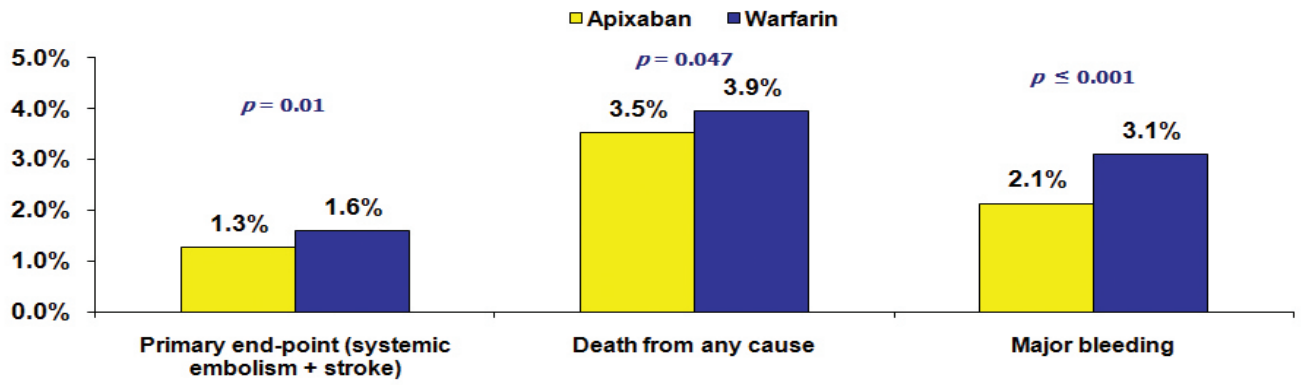
Corresponding Author: Ravi R. Kasliwal
Chairman, Clinical and Preventive Cardiology,
# 9, 3rd Floor OPD Block, Medanta-The Medicity, Sector 38,
Gurgaon, Haryana- 122001, India
Ph: +91-124-4141414 | Fax: +91-124-4834111
Email: rrkasliwal@hotmail.com

### ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation Study)

Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *NEJM.* 2011; 365:981–992.

## Trial summary

This was a multicenter, randomized, double-blind, double-dummy, trial to compare the use of apixaban (oral direct anti Xa inhibitor) to warfarin in patients with AF and at least one additional risk factor for stroke. This large trial included 18,201 patients of AF or atrial flutter, either ongoing or documented two or more episodes at least two weeks apart in the year before enrolment. In addition, the patients had at least one other risk factor for stroke ( age ≥ 75 years, previous stroke, transient ischemic attack, systemic embolism, symptomatic heart failure within previous 3 months, LVEF < 40%, diabetes mellitus, or hypertension requiring pharmacological treatment). The patients were randomized to receive fixed dose apixaban (5 mg twice daily or 2.5 mg twice daily for patients with any two of the following – age ≥ 80 years, weight < 60 kg, or serum creatinine ≥ 1.5 mg/dL) or adjusted-dose warfarin (target INR 2.0–3.0). The primary efficacy outcome was stroke or systemic embolism while the key secondary efficacy outcome was death from any cause. The primary safety outcome was major bleeding, while the secondary safety outcome was a composite of major bleeding and clinically relevant nonmajor bleeding. At the end of follow-up period (median of 1.8 years), the primary outcome of stroke or systemic embolism occurred in 212 patients in the apixaban group (1.27% per year) as compared to 265 patients in the warfarin group (1.6% per year) (hazard ratio in the apixaban group 0.79; $p<0.001$ for noninferiority and $p=0.01$ for superiority). The rate of hemorrhagic stroke was 45% lower, while ischemic




stroke was 8% lower in the apixaban group as compared to the warfarin group. The rate of death from any cause was lower in the apixaban group than in the warfarin group (3.52% vs. 3.94% per year; hazard ratio 0.89; $p$=0.047). The rate of death from cardiovascular causes, including death from hemorrhagic stroke, was 1.80% per year in the apixaban group and 2.02% per year in the warfarin group (hazard ratio 0.89; $p$=NS).

Major bleeding (defined as clinically overt bleeding associated with a fall in hemoglobin of at least 2 g/dL or transfusion of at least 2 units of packed red cells, occurring at a critical site or resulting in death) occurred in 327 patients in the apixaban group (2.13% per year) and in 462 patients in the warfarin group (3.09% per year) (hazard ratio 0.69; $p$<0.001). The incidence of fatal bleeding was also less in the apixaban group in comparison to the warfarin group (34 vs. 55 patients).

## Perspective

In this large clinical trial, fixed-dose apixaban (rapidly absorbed orally administered direct Xa inhibitor) has been shown to be superior to warfarin in preventing stroke or systemic embolism in patients of AF with additional risk factors for stroke. The primary effect was on reduction of hemorrhagic stroke and was consistent across subgroups according to age, gender, geographic region, degree of renal dysfunction, diabetic status, presence of heart failure, etc. Apixaban not only proved to be more efficacious as an anticoagulant, but also caused less bleeding and demonstrated mortality benefit.

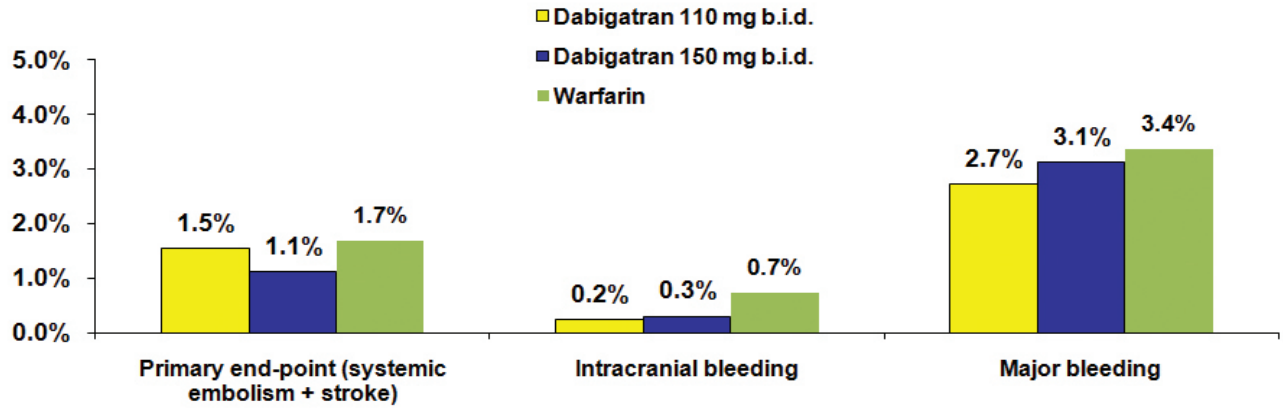
### RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy)

Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation *NEJM*. 2011;361:1139–1151.

## Trial summary

This was a study conducted to compare the efficacy and safety of two blinded doses of dabigatran etexilate (orally active, direct thrombin inhibitor) with open-label warfarin for the prevention of stroke and systemic embolism in patients with nonvalvular AF.

This large, noninferiority trial was conducted at 951 sites across 44 countries and recruited 18,113 patients of nonvalvular AF with an additional risk factor of stroke (previous stroke or transient ischemic attack, left ventricular ejection fraction <40%, New York heart association class II or higher heart-failure symptoms within previous 6 months, age of at least 75 years, or an age of 65–74 years plus diabetes mellitus, hypertension, or coronary artery disease). The patients received either dabigatran 110 mg twice daily or 150 mg twice daily in a blinded manner while warfarin was administered in an unblinded manner, adjusted locally to keep an INR of 2.0–3.0. The primary outcome was systemic embolism or stroke while the primary net clinical benefit outcome was the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction (MI), death, or major hemorrhage. Primary safety outcome was hemorrhagic stroke. Secondary outcomes were stroke, systemic embolism, and death.




At the end of the follow-up period (mean of 2 years), the primary outcome occurred at a rate of 1.69% per year in the warfarin group, compared to 1.53% in the dabigatran 110 mg group (relative risk with dabigatran, 0.91; $p<0.001$ for noninferiority) and 1.11% per year in the dabigatran 150 group (relative risk with dabigatran 0.66; $p<0.001$ for superiority). The rate of hemorrhagic stroke was 0.38% per year with warfarin; 0.12% per year in the dabigatran 110 mg group ($p<0.001$) and 0.10% per year in the dabigatran 150 mg group ($p<0.001$).

The net clinical benefit outcomes were 7.64% per year with warfarin, 7.09% per year with 110 mg dabigatran (relative risk 0.92; $p=0.10$), and 6.91% per year with dabigatran 150 mg (relative risk 0.91; $p=0.04$). The rate of major bleeding was 3.36% per year in the warfarin group, 2.71% per year in the group that received 110 mg dabigatran (relative risk 0.80; p=0.003), and 3.11% per year in the group that received 150 mg of dabigatran (relative risk 0.93; $p=0.31$). The rates of life-threatening bleeding and intracranial bleeding were higher with warfarin (1.8% and 0.74%) than that with either the 110 mg (1.22% and 0.23%) or 150 mg dabigatran (1.45% and 0.30%). The mortality rate was 4.13% per year in the warfarin group, as compared to 3.75% per year in the dabigatran 110 mg group ($p=0.13$) and 3.64% per year with 150 mg dabigatran group ($p=0.051$).

## Perspective

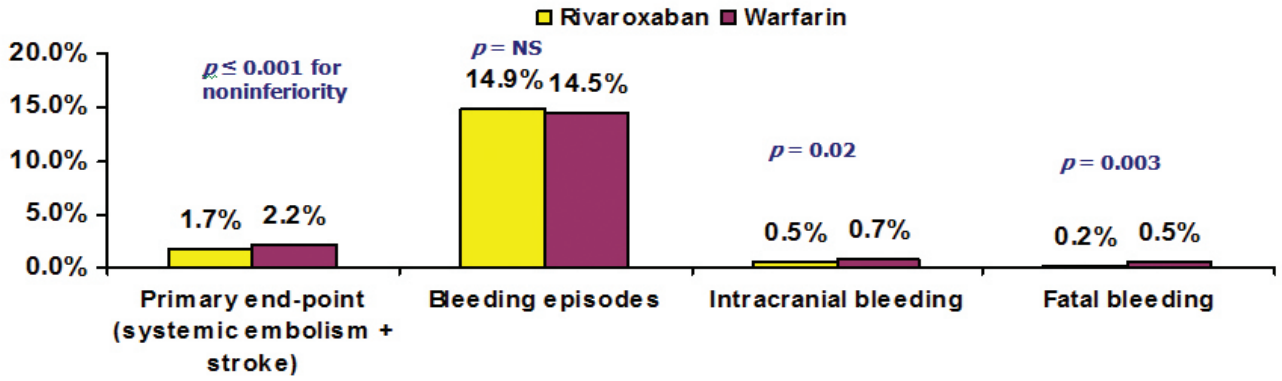
This trial demonstrated that both doses of dabigatran were noninferior to warfarin in preventing stroke and systemic embolism with the 150 mg dose even being superior to warfarin. Dabigatran in 110 mg dose also was shown to be superior to warfarin in preventing major bleeding. The rates of life-threatening bleeding and intracranial bleeding were also less with both doses of dabigatran as compared to warfarin with intracranial bleeding being less than one-third of the rate with warfarin.

### ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin-K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation)

Patel RM, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *NEJM*. 2011; 365:883–891.

## Trial summary

This was a multicenter, randomized, double-blind, double-dummy, event-driven trial to compare the use of rivaroaxaban (direct anti-Xa inhibitor) to warfarin in patients with nonvalvular AF. This large trial was conducted at 1178 sites across 45 countries and included 14,264 patients of nonvalvular AF at moderate to high risk of stroke (CHADS2 score of 2 or more). The patients were randomized to receive fixed-dose rivaroxaban (20 mg daily or 15 mg daily in patients with creatinine clearance 30–49 mL/min) or adjusted-dose warfarin (target INR 2.0–3.0). The patients in each group also received a placebo tablet so that blinding could be maintained. The primary efficacy end-point was the composite of systemic embolism and stroke (both embolic and hemorrhagic), while the secondary efficacy end-points included a composite of systemic embolism, stroke, or death from cardiovascular causes; a composite of stroke, systemic embolism, death from cardiovascular causes, and MI; and stroke, systemic embolism, death from cardiovascular causes, and MI separately. At the




end of follow-up period (mean of 707 days), the primary end-point occurred in 188 patients in rivaroxaban (1.7% per year) group and in 241 patients in the warfarin group (2.2% per year) (hazard ratio in the rivaroxaban group 0.79; $p<0.001$ for noninferiority). In the intention-to-treat analysis, the primary end-point occurred in 269 patients in the rivaroxaban group at a rate of 2.1% per year, while in the warfarin group it occurred in 306 patients (2.4% per year) (hazard ratio 0.88; $p<0.001$ for noninferiority and p=0.12 for superiority). Among the secondary end-points, MI occurred in 0.9% and 1.1% patients per year in the rivaroxaban and warfarin groups, respectively ($p=0.12$).There were 208 deaths in the rivaroxaban group (1.9% per year) and 250 deaths in the warfarin group (2.2% per year) (hazard ratio 0.85, $p=0.07$).

There was no significant difference in the incidence of major and nonmajor clinically relevant bleeding in rivaroxaban (14.9% per year) and warfarin (14.5% per year) groups ($p=0.44$). However, there was significant reduction in intracranial hemorrhage (0.5% vs. 0.7%, $p=0.02$) and fatal bleeding (0.2% vs. 0.5%, $p=0.003$) in the rivaroxaban group.

## Perspective

In this pivotal trial, rivaroxaban has been shown to be noninferior to warfarin in preventing strokes and systemic embolism in patients with nonvalvular AF at moderate-to-high risk for stroke. However, rivaroxaban failed to meet the superiority criteria in the intention-to-treat analysis. Significant reduction in intracranial and fatal bleeding demonstrated with rivaroxaban gives it a distinct advantage over warfarin for use in patients with AF.