January 2013

What are the new therapeutic alternatives to warfarin in atrial fibrillation?

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Why are the studies on these newer agents important?

Atrial fibrillation is associated with an increased risk of stroke (mean= 4.5% per year) and hence necessitates starting the patients on lifelong oral anticoagulants. Vitamin K Antagonists, like Warfarin, have been the mainstay of treatment, but remain grossly underused because of increased bleeding risk, variability in results and the need for therapeutic monitoring. The advent of newer agents like Dabigatran, direct factor IIa (thrombin) inhibitor and Apixaban and Rivaroxaban, Factor Xa inhibitors may make this a little easier. These fast acting, short lived, fixed dosed (unmonitored) agents exhibit limited drug and food interactions and provide consistent and predictable anticoagulation.

The Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial evaluated the efficacy and safety of two doses of Dabigatran relative to Warfarin in patients with atrial fibrillation. The Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET AF) trial compared the outcomes of Rivaroxaban (20 mg /day) and dose adjusted Warfarin. Apixaban (2.5 mg BID) was also compared with aspirin (81-324 mg QD) for stroke prevention in AF Apixaban Versus Acetylsalicylic Acid to Prevent Strokes (AVERROES) trial.

This review highlights the main findings in these three trials and presents a brief comparison of the efficacy of Warfarin against Dabigatran, Apixaban and Rivaroxaban.

Who were the study participants?

RE-LYenrolled and followed 18,113 elderly patients (mean age: 71.6 ± 8.7 years) from 44 countries in the 2-year largest ever randomized controlled trial of antithrombotic therapy. Subjects had a mean CHADS2 2.1 ± 1.1 and apart from atrial fibrillation had one other stroke predisposing risk factor : (previous stroke or TIA, left ventricular ejection fraction < 40%, New York Heart Association heart failure classification of II or higher, age ≥ 75 years, or age 65-74 years plus diabetes mellitus, hypertension, or coronary artery disease). History of stroke within 14 days or a severe one in past 6 months, increased bleeding risk, active liver diseases, creatinine clearance < 30mL/min were some of the exclusion criteria.

The ROCKET AF trial enrolled 14,264 patients (mean CHADS2>3.5) with non valvular atrial fibrillation and 55% of them were positive for a history of stroke, TIA or systemic embolism at the start of the study (median time 707 days).

The AVERROES trial recruited 5, 599 subjects (mean age 70 years) non valvular atrial fibrillation patients in whom Vitamin K antagonists were contraindicated and they had a mean CHADS2 of 2. 86% did not have a previous stroke or TIA.

What was the intervention?

In RE-LY trial, out of 18,113study participants 6,022were randomly assigned to either receive adjusted-dose Warfarin, with INR target 2.0 to 3.0, monitored monthly. 6,015 subjects were administered Dabigatran 110 mg BID and 6,076 received Dabigatran 150 mg BID. The categorization employed double blinding.

In ROCKET AF trial, 14,264 patients with non valvular atrial fibrillation were either administered Rivaroxaban (20 mg/dL) or dose-adjusted warfarin (target INR 2.0-3.0).

In the AVERROES trial, subjects were randomly assigned to receive 5mg Apixaban BID or a lower dose 2.5 mg BID if the patient had age ≥ 80 years, weight ≤ 60 kg or serum creatinine ≥ 1.5 mg/dL. Doses of Aspirin administered were 81 mg (64%), 162 mg (27%), 243 mg (2%) or 324 mg (7%). Study participants were noted for occurrence of ischaemic or haemorrhagic events and systemic embolism. Study subjects had a mean CHADS2 ? 2 with 14 % positive for a history of prior stroke.

What were the findings?

Study participants were noted for primary end point i.e. ischaemic/haemorrhagic stroke and systemic embolism.

Dabigatran, 150 mg BID and 110 mg BID, exhibited lesser incidence of stroke and systemic embolism (1.11% /year and 1.53% /year) compared to warfarin (1.69%/year). Net clinical benefit showed higher RR 7.09% per year for Warfarin and Dabigatran 110 mg compared to 6.91% per

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yearfor Dabigatran 150 mg. Mortality with Dabigatran 150 mg BID (3.64% year) was lowest overall when compared to warfarin (4.13% per year; RR, 0.88; 95% CI,0.80-1.03) and Dabigatran 110 mg BID (3.75%; RR,0.91; 95% CI, 0.80-1.03). However, major bleeding was lowest (2.71 % per year) with Dabigatran 110mg BID compared to Warfarin (3.36 % per year) and Dabigatran 150 (3.11 % per year).

The ROCKET AF trial showed that 14.9% of patients per year in the Rivaroxaban group and 14.5% in thewarfarin groupwere complicated with non-major and major clinical bleeds. Rivaroxaban administration was also associated with net benefiti.e. an overall primary end point incidence of 2.5 % compared to Warfarin (3.61 %) in subjects with history of prior stroke, TIA or systemic embolism.

AVERROES trial attested to the superiority of Apixaban over Aspirin therapy with incidence of stroke or systemic embolism 1.67 % and 3.7 % per year. Net clinical benefit of Apixaban was 5.3% per year and that of Aspirin was 7.2% per year. In patients who had previously taken Vitamin K antagonist, Apixaban was more effective in preventing stroke or systemic embolism, the incidence being 1.4 % as opposed to 4.2 % per year for Aspirin.

What were the conclusions?

These agents were comparable in efficacy overall and better in safety profile in patients without renal failure compared to warfarin, albeit at high cost.Based on the trials some newer international recommendations (AHA guidelines) emerged and are hence noteworthy. Warfarin (1A), Dabigatran (1B), Apixaban (1B) and Rivaroxaban (IIa B) were all indicated for stroke prevention in patients with non valvular atrial fibrillation.

How does this affect clinical practice in Pakistan?

These agents are certainly useful in selected populations. It must be remembered that missing a dose equates with being non anticoagulated due to the shorter half-life of these agents. The safety of combining Dabigatran, Rivaroxaban, or Apixaban with an antiplatelet agent has not been established. Reversal also is of concern in bleeding scenarios. Use of Factor VII, cryoprecipitate or emergency dialysis has been proposed. Cost will be a significant barrier in resource poor areas; although studies may reveal that they may be eventually cost effective due to less money spent on tests, anticoagulation clinics avoiding strokes and bleeds. These studies must be performed locally before these medicines can be widely recommended regionally.

Acknowledgements and Disclosures:

There are no relevant conflicts of interest to declare with regards to this review.

Recommended Reading:

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