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A REVIEW TO ASSESS THE ESSENCE AND CHALLENGES OF NEWER ORAL ANTICOAGULANT THERAPY FOR ATRIAL FIBRILLATION

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ABSTRACT

Atrial fibrillation is a common type of arrhythmia, particularly seen in older individuals. Stroke is a major complication associated with atrial fibrillation. In the year 2050, Asia will have 72 million atrial fibrillation patients and 2.9 million among them will suffer from atrial fibrillation-associated stroke. The recent advent of newer oral anticoagulants presents a promising future for anticoagulant therapy, especially for Indian atrial fibrillation patients. But it is also associated with a number of predicaments. Our literature review mainly explores the complexities of newer oral anticoagulant therapy based on current studies.

KEYWORDS: arrhythmia, atrial fibrillation, anticoagulant therapy, oral anticoagulant.

INTRODUCTION

Warfarin is a vitamin K antagonist that has been used traditionally for the prevention of stroke in non valvular as well as valvular atrial fibrillation patients. But recently, newer oral anticoagulants (NOACs) such as Dabigatran, Riveroxaban and Apixaban were introduced in India for the thromboprophylaxis treatment of non valvular atrial fibrillation patients. So this makes the anticoagulant therapy in such a scenario, more challenging and intriguing. Eventhough the NOACs are now widely used as an alternative to warfarin in atrial fibrillation patients, studies done on an Indian population is limited. So our literature review mainly focuses on the current challenges as well as advantages of NOAC therapy from an Indian perspective.

NEWER ANTICOAGULANTS

Dabigatran, Riveroxaban and Apixaban are the three prominent newer oral anticoagulants that are available now in India. Dabigatran is a thrombin inhibitor. So it works by inhibiting thrombin. Once this happens, the conversion of fibrinogen to fibrin will also get inhibited. Thus this will further inhibit the activation of factor V, VIII, XI, XIII and the platelets. Riveroxaban and Apixaban are factor Xa inhibitors. So they works by the direct inhibition of factor Xa.

Efficacy, safety and dosing

All three of the newer anticoagulants have shown its non inferiority against warfarin in Large randomized clinical trials (RE-LY, ROCKET AF and ARISTOTLE).[1-3] Figure (1), (2) and (3) depicts the difference in rate of stroke and bleeding events per year in all 3 large randomized clinical trials of newer anticoagulants against warfarin. In RELY trial, 150 mg and 110 mg of dabigatran was compared with that of dose adjusted therapy of warfarin. The 150 mg of dabigatran produced better efficacy in reducing the rates of stroke and systemic embolism but produced similar rates of major haemorrhage as that of warfarin. The 110 mg of dabigatran was associated with similar rates of stroke and systemic embolism but the rate of major haemorrhage were less when compared to warfarin. The only adverse effect that was found more in dabigatran was dyspepsia. So, from the RELY study, we can conclude that 110 mg of dabigatran might be dose that will be effective for Indian patients. This is mainly because of the fact that the risk of bleeding, especially intracranial haemorrhage is higher in Asians than in Caucasians.[4] So lower dose of a newer anticoagulants that produces less adverse effects must be preferable for Indian patients. In a large Chinese population study by Wen-Hua Li et al, which compared riveroxaban, dabigatran and warfarin, 110mg dabigatran had an additional 57% stroke reduction rate when compared to warfarin.[5] This observation is consistent with the RE-LY Asian substudy showing that dabigatran 110 mg twice daily was associated with a lower risk of ischemic stroke compared with warfarin.[6] This particular asian substudy of RE-LY trial by Hori M et al also showed that total bleeding and hemorrhagic stroke rates in Asian patients on warfarin were significantly higher than in

non-Asians. Finally, there was a statistically significant reduction in bleeding outcomes by dabigatran more in Asians than in non-Asians. This once again reiterates the essence of a lower dose of dabigatran (110mg) for Indian patients.

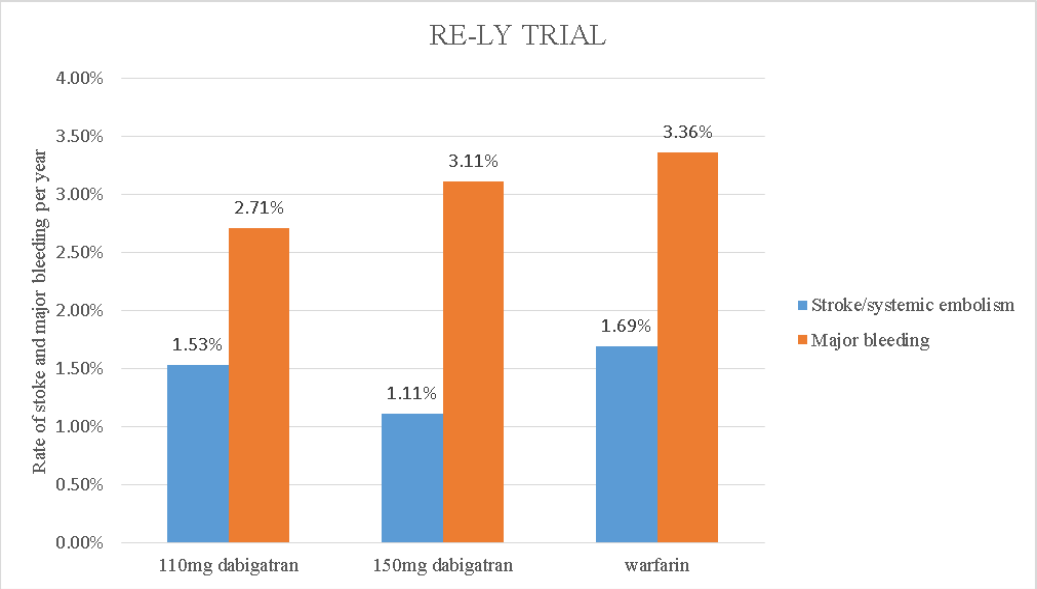

Figure (1): Rate of stroke/ systemic embolism and bleeding events per year in RELY trial.

Aristotle trial by Christopher B. Granger et al, was the main large randomized control trial of apixaban which compared apixaban 5mg with warfarin.[3] Lower dose of 2.5mg apixaban was only used in patients above 80 years of age and for patients with body weight below 60Kg or for patients with abnormal creatinine clearance. The rate of stroke or systemic embolism were less in patients taking apixaban as compared to patients taking warfarin. According to the Aristotle trial, the rate of hemorrhagic stroke were 49% lower in the apixaban group than in the warfarin group, and the rate of ischemic or uncertain type of stroke were 8% lower in the apixaban group than in the warfarin group. Major bleeding outcomes also occurred less in the apixaban group as compared with the warfarin group. In an East Asian specific subgroup analysis of ARISTOTLE trial by Shinya Goto et al, apixaban produced similar rates of stroke reduction and major bleeding in East Asians as well as non Asians.[7] So unlike dabigatran 110mg, apixaban reduced bleeding and stroke similarly in both Asians as well as non Asians. However there is a lop-sidedness in the proportion of East Asians to that of non- Asians in that particular study.

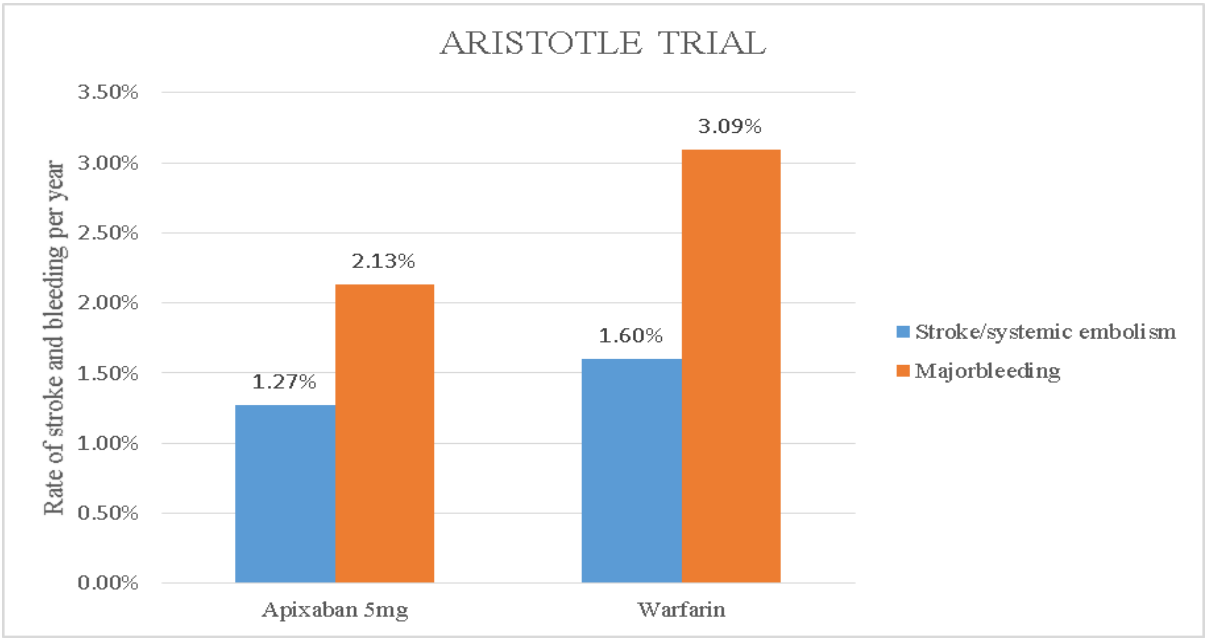

Figure (2): Rate of stroke/ systemic embolism and bleeding events per year in ARISTOLE trial.

In the large randomized study of riveroxaban (ROCKET-AF trial) by Manesh R. Patel et al, Riveroxaban, like the other two newer anticoagulants, reduced rate of stroke or systemic embolism when compared to warfarin. But the amount of bleeding outcomes were similar in both the riveroxaban and warfarin group, though, rate of intracranial haemorrhage were significantly less in the riveroxaban group. ROCKET- AF TRIAL mainly used 20mg riveroxaban for their study population. 15mg riveroxaban was only used for patients with abnormal creatinine clearance. This findings is consistent with the real world study on Chinese atrial fibrillation patients by Wen-Hua Li et al.[8] Riveroxaban 20mg had the least number of intracranial heammorhage. But the striking difference between ROCKET- AF trial and this study comes, in the case of 15mg riveroxaban. 15mg riveroxaban had the highest intracranial haemorrhage in the Wen-Hua Li et al study. But this particular data was based on numerical number of events alone. Further studies needs to done to assert the difference in effect of riveroxaban when it comes to a lower dose (15mg) and higher dose (20mg). Statistically, however, 20 mg riveroxaban produced a significantly lesser number of annual incidence of stroke when compared with 15mg.

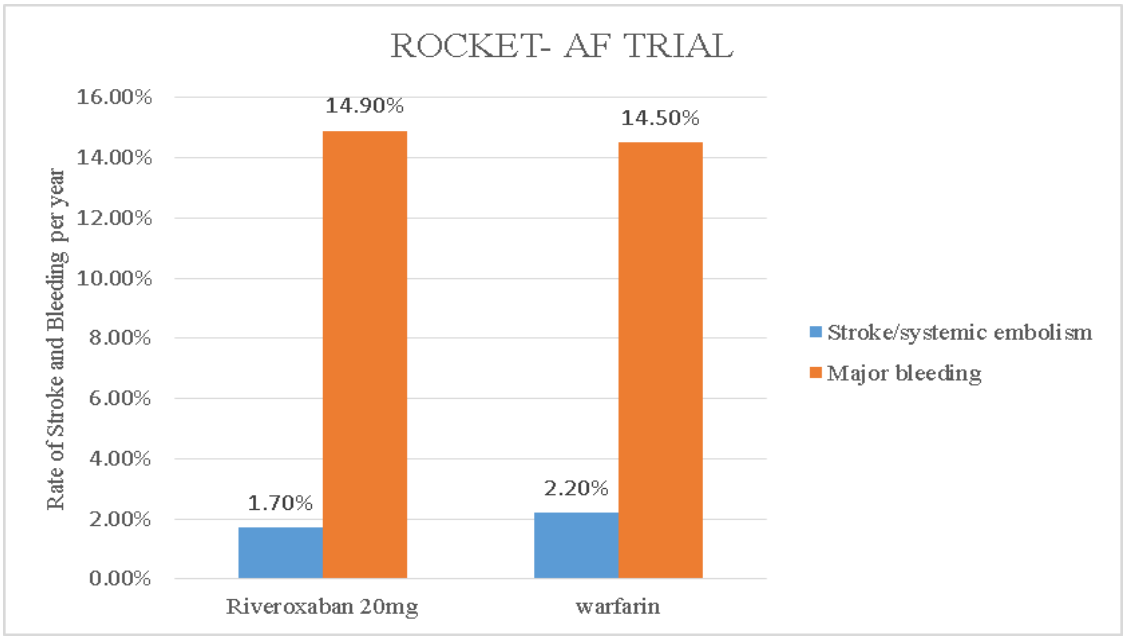

Figure (3): Rate of stroke/systemic embolism and bleeding events per year in ROCKET- AF trial.

Among the direct comparison studies between the three newer anticoagulants by Peter A. Noseworthy et al, found that, all three of the newer anticoagulants have similar effectiveness. But interms of bleeding, apixaban was associated with lower risk and riveroxaban was associated with a higher bleeding risk.[9] This finding is consistent with the indirect comparison study of newer anticoagulants by Schneeweiss S et al.[10] 2017 study by Myung-Jin Cha et al, once again reiterates this finding. Myung-Jin Cha et al study which was based on Korean population, found that, all three of the newer anticoagulants were associated with similar risk of ischemic stroke but apixaban and dabigatran were associated with lower risk of mortality and intracranial haemorrhage.[11] So, based on the present studies, apixaban 5mg and dabigatran 110mg remains as the viable drugs for anticoagulation for Indian atrial fibrillation patients, especially, when the risk of bleeding is taken into consideration.

Monitoring

Unlike warfarin, one of the major advantages of newer anticoagulants is that, it does not require any constant monitoring. However, monitoring of their activity is essential in special situations such as in perioperative settings or during a suspected overdose situation. Classical coagulation tests can be misleading for determining its anticoagulant activity. In a systemic review which was done by Cuker A et al, summarises the sensitivities of the newer anticoagulants against various coagulation tests.[12] It was found that, dabigatran was too intensely sensitive to thrombin time (TT) or thrombin clotting time (TCT) whereas activated partial prothrombin time (APTT) and prothrombin time (PT) showed poor sensitivity. Only ecarin clotting time (ECT), ecarin chromogenic assay (ECA) and dilute thrombin time (dTT) showed high degree of sensitivity for dabigatran. In the case of riveroxaban and apixaban, anti Xa was the only assay which showed linear sensitively against various concentrations, though, PT and APTT was prolonged by apixaban with an insufficient sentisitivity to draw conclusions. This particular finding is consistent with the study done by Douxfils J et al.[13] Douxfils J et al concluded that none of classical coagulation tests such as PT and aPTT, are useful at all and those test can lead to misinterpretation. Only chromogenic anti-Xa assays and a dilute thrombin time should be recommended for the assessment of

newer oral anticoagulants. So, for monitoring of NOACs, specific quantitative calibrated assays are required rather than classical coagulation tests. This is presents a difficult situation, especially for real world clinical practice in India, because of the limited number of availability of these assays and tests in hospitals of India.

Table (1): Different types of test to determine anticoagulant activity

Drug	Reliable Test
Dabigatran	Ecarin clotting time Ecarn chromogenic assay Dilute thrombin time(dTT)
Riveroxaban	Chromogenic anti- Xa assay
Apixaban	Chromogenic anti- Xa assay

Lack of reversal agents

Vitamin K can be used for reversing the effects of warfarin induced bleeding. But for NOACs, there's a lack of specific reversal agent (except for dabigatran). Generally, nonspecific agents such as prothrombin complex concentrate (PCC) and activated prothrombin complex concentrate (aPCC) are used as reversal agents for NOAC induced bleeding. These nonspecific reagents are also used for management of warfarin induced bleeding, inorder to get immediate effects. A literature review by Mosaad Almegren in 2017, discussed various specific as well as nonspecific agents for reversing the effects of vitamin k antagonist as well as NOACs. [14] According to this particular study, 50 U/kg and 25 U/kg of PCC was able to reverse the effects of 20mg riveroxaban and apixaban 5 mg while it was unable to do so in the case of 150mg dabigatran. In the case of activated prothrombin complex concentrate, the current studies remains inconclusive.[14]

Idarucizumab is the only FDA approved specific reversal agent that is used for the reversal of bleeding caused by dabigatran. The RE-VERSE AD study in 2017, found out that the, uncontrolled bleeding caused by dabigatran in more than 98% patients in that study population was reversed by idarucizumab.[15] A single 5 g of idarucizumab was able to reverse the bleeding in more than 98% patients with elevated ECT and dTT. Another advantage of this particular study was the rate of thrombosis. The rate of thrombosis in patients were much lesser when compared with other studies which involves patients treated with prothrombin complex concentrate. [16] This clearly indicates the superior reversal ability of idarucizumab against nonspecific reversal agent (prothrombin complex concentrate). Other specific agents are also available but studies associated with them are limited.

Table (2): Reliable reversal agents for each newer anticoagulant

Drug	Reliable reversal agent
Dabigatran	Idarucizumab
Riveroxaban	Prothrombin complex concentrate (50 U/kg)
Apixaban	Prothrombin complex concentrate (25 U/kg)

ADHERENCE

Since anticoagulant drugs are associated with severe adverse bleeding events and stroke, adherence to these medications is one of the pivotal aspects of the therapy. Though several studies have reported the better adherence of newer anticoagulants when compared to warfarin, head to head direct comparison among the NOACs is limited. Joshua D. Brown et al study included real world analysis of adherence to NOACs. That particular study concluded that, riveroxaban and apixaban had better adherence profiles than dabigatran.[17] These findings are consistent with Faris Al-Khalili et al study. [18] Faris Al- Khalili et al also found out that riveroxaban and apixaban showed similar but high adherence in non valvular atrial fibrillation patients. However, they did not include dabigatran in their study. Another factor when it comes to adherence is the dosing regimen of the drug. Riveroxaban is expected to produce better adherence in patients, especially, for those who prefer low pill burden. This is because of once daily dosing regimen of riveroxaban when compared to twice daily in apixaban and dabigatran. But Xiaoxi Yao et al study in 2016, which compared all three of the newer anticoagulants and found out that, such an advantage does not exist at all for riveroxaban. Instead apixaban was the drug that was associated with a much better adherence. [19] Xiaoxi Yao et al study also pointed out the fact that, patients who were non adherent to the medications because of their failure to refill rather than missing to take these medications on time. This can be associated with the cost of newer anticoagulants. The cost of newer anticoagulants are high when compared to that of warfarin. This could be a problem, especially for a country like India. Number of studies have reported the cost effectivesness of NOACs when compared to warfarin. Anuj Shah et al in 2016, found out that apixaban was the most cost effective anticoagulant. [20] However, since there is a lack of cost effective analysis studies, especially from India, it is hard to draw conclusions in this regard.

CONCLUSION

Our review mainly focuses on different aspects of treatment related to newer oral anticoagulants. In terms of efficacy and safety, apixaban 5 mg and dabigatran 110 mg can be considered as the viable option for Indian atrial fibrillation patients since current studies shows that riveroxaban users are at a higher risk of bleeding than other newer anticoagualnts. This is especially important because of the fact that risk of bleeding is higher in Asians than in caucasians. Eventhough newer anticoagulants does not require constant monitoring of its anticoagulant activity like warfarin, its activity has to be monitored in special situations like in perioperative settings. In such situations, classical coagulation test such as Prothrombin time and activated thrombin time are useless for determining its activity. Only Chromogenic anti Xa assays can detect the activity of riveroxaban and apixaban. In the case of dabigatran, Ecarin clotting time, dilute thrombin time and ecarin

chromogenic assay are the only ones that can be used reliably to detect its activity.

Reversing the bleeding caused by newer anticoagulants is another challenge in NOAC therapy. Till date, idarucizumab is the only FDA approved specific reversal agent for dabigatran and Prothrombin complex concentrate is the only nonspecific agent that can reverse the bleeding of apixaban and riveroxaban. Though other specific as well as nonspecific agents are available, studies associated with them are extremely lacking. Another crucial aspect of anticoagulant therapy is the medication adherence of the patients. From various studies, we could say that apixaban was the superior drug in this regard. However, direct comparison studies interms of cost, from India, is crucial inorder to completely understand the cost effectiveness of each NOAC for Indian atrial fibrillation patients.

Overall, although NOACs have shown promising results against warfarin, NOAC therapy still presents a number of challenges. Lack of a proper specific reversal agent and monitoring tests are the major drawbacks of NOACs. Among the 3 newer anticoagulants, based on the current studies associated with efficacy, safety, monitoring and adherence, Apixaban can be said as the most reliable drug for Indian atrial fibrillation patients. Apixaban has similar efficacy and better safety than riveroxaban. It is also said to be the superior drug in terms of medication adherence when compared with the other two NOACs. The only drawback of apixaban is the lack of conventional blood test for determining its anticoagulant activity. Though it lacks a specific reversal agent like dabigatran, Prothrombin complex concentrate has been shown to reverse its activity. Further studies needs to be done inorder to produce more robust evidence regarding the NOAC therapy in Indian atrial fibrillation patients.

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