Stroke Prevention in Atrial Fibrillation – Which is the BEST?: Balanced in Efficacy and Safety as a Thromboprophylactic

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Abstract

Stroke prevention in atrial fibrillation (AF) has reached an exciting phase with a plethora of newer, potentially more efficacious and safer agents being introduced for physicians to select from. Dabigatran belongs to a class of anticoagulants called direct thrombin inhibitors, while rivaroxaban, apixaban, and edoxaban are direct Factor Xa inhibitors. Purely from a therapeutic endpoint perspective—based on the action of anticoagulants in reducing cardioembolic stroke—in clinical trials, one should look at whether a new anticoagulant in patients with AF prevents ischemic stroke. From a net clinical benefit perspective, one evaluates both efficacy and safety, which is when one includes association of stroke prevention with: hemorrhagic stroke; major, intracranial, life-threatening or total bleeding, etc. Interestingly, so far only dabigatran 150mg bid has been shown to be superior to well controlled warfarin in reducing the risk of ischemic stroke in patients with AF. Apixaban 5 mg bid, dabigatran 110 mg bid and both doses of edoxaban were superior to well controlled warfarin in being associated with a lower incidence of major bleeding. Apixaban 5 mg bid and edoxaban 30 mg od were superior to well controlled warfarin in reducing all-cause mortality. Clinicians will need to judiciously prescribe the right drug for the right patient, keeping many factors in consideration, and individualize the therapy based on underlying comorbidities and response to therapy.

Pivotal trials of NOACs in SPAF

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial (a Prospective, Randomized, Open, Blinded End-point [PROBE] design) was the first to demonstrate that a new oral anticoagulant, dabigatran etexilate, was not just non-inferior, but actually superior at a dose of 150 mg bid to well controlled (median cTTR 67%) warfarin in preventing ischemic stroke/systemic embolism and reducing vascular mortality while being associated with significantly reduced incidence of hemorrhagic stroke, and intracranial, life-threatening, or total bleeding. Next in line was the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), where rivaroxaban was shown to be non-inferior to not-so-well-controlled (median cTTR 58%) warfarin. This was followed by Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE), in which apixaban was found to be superior to well controlled (median cTTR 66%) warfarin in being associated with significantly lesser hemorrhagic stroke, major bleeding, and all-cause mortality. The results of the edoxaban trial, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation—Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48), which recruited more than 20,000 patients, are now published and edoxaban was not superior to well controlled (median cTTR 68%) warfarin in the primary efficacy endpoint, but significantly safer (30 mg and 60 mg once daily) in terms of major bleeding and significantly better (30 mg once daily) in reducing all-cause mortality.

Direct Thrombin Inhibition

Dabigatran belongs to a class of anticoagulants called direct thrombin inhibitors (DTIs). Others in this class preceding dabigatran are efegatran, inogatran, sofigatran, and ximelagatran. Parenteral DTIs include bivalirudin, hirudin, and lepirudin. DTIs, as the name suggests, inhibit thrombin or factor IIa directly, competitively, and reversibly. Thrombin has multiple
actions and its inhibition in turn leads to inhibition of thrombin-induced platelet aggregation, thrombin-induced activation of factors V, VIII, and XI, thrombin-induced stabilization of the fibrin clot via factor XIII, thrombin-mediated actions on thrombin-activatable fibrinolysis inhibitor, protease activated receptors on platelets, and thrombomodulin. In fact, a DTI has been shown in in vitro studies to be anti-inflammatory, to have remodeling effects that reduce the arrhythmogenic substrate for thromboembolism, and to be anti-fibrotic and anti-proliferative. In vitro data need not necessarily correlate with in vivo results. The goal of any anticoagulant is to inhibit pathological thrombosis without interfering with physiological hemostasis. However, one may not be able to be so specific or selective. As a result, with any anticoagulant, while bleeding is not always directly caused by the anticoagulant, when a patient bleeds for any reason—for example, trauma, hypertension-induced shear stress, concomitant use of coagulation-affecting drugs, e.g., nonsteroidal anti-inflammatory drugs, aspirin, clopidogrel—bleeding does take a longer time to stop versus if the patient was not taking an anticoagulant.

However, not being on the anticoagulant increases the risk of a devastating ischemic stroke due to AF. Hence it is important to balance the risk of stroke and the risk of bleeding against the benefit of stroke prevention and the risk of not being on the anticoagulant. Compared with the bivalent parenteral DTIs such as bivalirudin, which binds to both the exosite I and the active site on thrombin, dabigatran is a univalent oral DTI that binds to only the active site on thrombin. This means that some thrombin is available for platelet aggregation if required to arrest bleeding. Thrombin is at the fulcrum of procoagulant and anticoagulant pathways and is the ultimate step in converting fibrinogen into fibrin. In AF, the stasis of blood in the left atrial appendage is one factor in Virchow’s triad that predisposes the patient to thrombus formation, but there is also evidence of endothelial dysfunction and hypercoagulability.

Incidentally, an anticoagulant, when used in AF, cannot prevent hemorrhagic stroke; it can
only prevent ischemic stroke. Hemorrhagic stroke is not caused by AF per se but can happen because of the side effect of the anticoagulant, or because of concomitant uncontrolled hypertension in AF patients due to age-related loss of elasticity of the arteries, or because of head injury. So, as a primary efficacy endpoint in clinical trials, one should focus on whether a new anticoagulant in AF prevents ischemic stroke. From a net clinical benefit perspective, one evaluates both efficacy and safety, which is when one includes association with hemorrhagic stroke, and major, intracranial, life-threatening, or total bleeding, etc. Interestingly, thus far only dabigatran 150 mg has been shown to be superior to well controlled warfarin in preventing or reducing the risk of ischemic stroke in AF patients. Apixaban 5 mg bid was also 21% superior to well controlled warfarin in reducing the risk of stroke, but the reduction in ischemic stroke was only 8% (not significant) and the reduction in hemorrhagic stroke was 49%, which drove the 21% difference.

**Factor Xa Inhibitors**

Factor Xa inhibitors such as rivaroxaban, apixaban, and edoxaban are the other class of new oral anticoagulants that have come to the market. As shown in the figure (Fig. 1), they act on inhibiting factor Xa directly, competitively, and reversibly, at the intersection of the intrinsic and extrinsic pathways of coagulation. Thus, they inhibit downstream effects of factor Xa, which means no formation of prothrombin or no conversion of prothrombin to thrombin. It has been hypothesized that this may be a reason why factor Xa inhibitors may be associated with lower MI rates. However, even with dabigatran, it is not that dabigatran causes more MI than warfarin. A more accurate way of reading the evidence is that both warfarin and dabigatran reduced MI, but warfarin did it a shade better than dabigatran. Rivaroxaban’s once daily dosage may be perceived to offer a compliance advantage but the peak to trough variability with a once daily vis a vis a twice daily dosing may mitigate that advantage.

 Naturally, doctors would want to debate on which is better, factor IIa or factor Xa inhibitors, from both an efficacy and safety perspective; hence the title of this article. However, for obvious reasons, it is highly unlikely that companies would sponsor trials comparing a factor IIa inhibitor with a factor Xa inhibitor. Clinicians will need to determine to which drug, or regimen, will an individual patient respond the best. Perhaps this is best done by the randomized controlled N of 1 trial, but in practice this is not feasible. Clinical acumen is challenged, and it is here that in-depth analysis of respective trial databases to predict clinical biomarkers of efficacy and safety may help doctors match the right patient to the right drug.

**Factor IIa or Factor Xa Inhibitors – 2A or not 2A, that is the Question?**

Until this happens, there will be endless debates on which is better, when actually the moot question is, how does one decide which patient responds best to which medicine? Proponents of factor Xa inhibitors say that this class is safer, as thrombin is not inhibited and therefore available for hemostasis if and when required. Apixaban 5 mg bid was 31% superior in being associated with a lower incidence of major bleeding as compared to well controlled warfarin. Dabigatran 110 mg bid was also superior to well controlled warfarin in being associated with a lower incidence of major bleeding. Inhibition of factor Xa also means no thrombin will be formed. So, does this predispose a patient to more bleeding? In an ACS setting (higher risk of bleeding as dual anti-platelet therapy is added on to the anticoagulant) two trials on factor Xa inhibitors (APPRAISE-2, RUBY-1) had to be prematurely terminated due to excess bleeding in patients randomized to the factor Xa inhibitor arm. In the ATLAS ACS TIMI-51 trial too, rivaroxaban in higher doses was associated with more bleeding, though the 2.5 mg bid dose fared better.

Can a drug inhibit thrombin formation totally? Will the body not ensure that some thrombin, if and when required, is always formed despite presence of the factor Xa inhibitor? With any drug eventually there is always a state of equilibrium that forms with the body’s compensatory homeostatic mechanisms such that the drug acts to inhibit the pathologic state while leaving physiologic systems relatively unaffected.

On the other hand, with a factor IIa inhibitor, thrombin is inhibited, which is the final step in clotting, so from an efficacy point of view this class would seem to be the most potent. Is there a bypass pathway such that even when factor Xa is inhibited, thrombin is somehow still formed? The accompanying figure may seem to indicate this (factor V to factor Va, which can also convert prothrombin to thrombin) but more substantiation of this hypothesis is needed. Then, a factor Xa inhibitor may not be as potent as a factor IIa inhibitor, somewhat like the difference between an ACE inhibitor and an angiotensin receptor blocker? However this is at best conjectural and the proof of the pudding is in the eating. Clinical trials have shown that both factor IIa and factor Xa inhibitors have advantages over well controlled warfarin. Having said this, let us also remember that well controlled warfarin was itself shown to be 64% better than placebo in reducing the risk of stroke and 24% better than placebo or aspirin in reducing all-cause mortality.
Safety of the NOACs

The other question is whether the direct thrombin inhibitor class is associated with more bleeding? Dabigatran competitively and reversibly inhibits only the active site on thrombin, not the exosite, thus leaving some thrombin available to induce platelet aggregation if and when needed. In any case the amount of thrombin needed to activate platelets is much less than that needed to convert fibrinogen to fibrin. RE-LY proved that dabigatran was quite safe at both the doses studied, although the 110 mg twice-daily dose was associated with significantly less intracranial hemorrhage, hemorrhagic stroke, and life-threatening, major, or total bleeding. Interestingly, among centers where the time in therapeutic range (TTR) was below the median (67%), dabigatran 150 mg bid was superior to well-controlled warfarin in all three parameters, viz., stroke/SEE, major bleeding and all-cause mortality. In India the TTR was only 49%. But this could be construed as cherry picking of the data. The only bleeding that was significantly more in the dabigatran 150 mg twice-daily arm was gastrointestinal bleeding, not the feared intracranial hemorrhage, and the reason for this is as yet unknown. There was a significant interaction between age and dabigatran treatment regarding extracranial bleeding and, because of that, dabigatran 150 mg bid is not recommended in AF patients aged > 80 years. Given that the prevalence of AF sharply increases with age, and that age is the second strongest risk factor for stroke, it appears that many AF patients at high risk of stroke cannot take the advantage of dabigatran 150 mg b.i.d. efficacy because of the safety concerns. In addition, the elimination of dabigatran is much more dependent on the renal function than the elimination of any other NOAC, which may strongly influence the choice of NOAC in daily clinical practice.

Vitamin K Antagonists – Old is Gold?

The tug of war(farin) over more than 60 years will not be overcome by the new oral anticoagulants overnight, and will need years of education and behavior change to ensure patients are either on well controlled warfarin or one of the newer oral anticoagulants. Interestingly, is anyone well controlled on warfarin? International normalized ratio (INR) testing once a month gives a reading only at that point in time, not over 24 hours that day, nor over the month. Even if patients are within the recommended INR range of 2.0 to 3.0, in two-thirds of cases, one might have an intracranial bleed or a stroke. However, warfarin can still hold its own against this onslaught of newer non vitamin K antagonist oral anticoagulants (NOACs). It is not renally excreted and can be given to patients with a creatinine clearance of less than 30 ml/min, when the NOACs are not recommended by guidelines. It has a long biological effect half-life and even if a patient misses a dose, it still confers protection. It is dosed once daily which is convenient and facilitates compliance. In valvular AF patients (rheumatic mitral stenosis, prosthetic heart valves), only warfarin can be used. The phase II RE-ALIGN trial which evaluated dabigatran in patients with mechanical heart valves had to be prematurely terminated for safety and efficacy reasons. The factor VIIa-TF inhibition by warfarin is hypothesized to stabilize the atheromatous coronary plaque and make it cardioprotective. Warfarin’s acquisition cost in India is much lower than that of the NOACs, yet patient compliance is irregularly irregular.

Conclusion

Clinicians will need to select judiciously the right patient for the right drug, keeping many factors in consideration, above all the individuality of the patient and the way he or she expresses the disease and responds to drugs. In this connection, perhaps it is good if a drug is available in more than 1 dose as is the case with dabigatran etexilate and edoxaban. On the other hand, one dose for most indicated patients and a lower dose for some with pre-defined risk factors (e.g., based on age, weight, and/or renal function) may be simpler for doctors. Be that as it may, the advent of NOACs (no axe to grind with warfarin) may have changed the world of anticoagulation for the better. But it also throws up new challenges. Both doctors and patients didn’t want the headache of having to monitor VKAs with INR testing, but now that one does not need to monitor the NOACs there is a clamor for measuring the effects of NOACs. Vitamin K is an antidote for warfarin yet bleeding associated with warfarin (intracranial hemorrhage is more frequent) is more difficult to manage than that associated with NOACs (antidotes are being developed, e.g., idarucizumab for dabigatran, andexanet alfa for factor Xa inhibitors and ciraparantag for both factor IIa and Xa inhibitors). The more things change the more they remain the same. But medicine is an art and a science and must inexorably progress.

Summary

- In providing anticoagulation for patients with atrial fibrillation (AF), it is important to balance the risk of stroke and the risk of bleeding with the benefit of stroke prevention and the risk of not being on the anticoagulant.
- Thrombin is at the fulcrum of procoagulant and anticoagulant pathways and is the ultimate
step in converting fibrinogen into fibrin.

- While one is at risk of bleeding when one is on an anticoagulant, often the bleeding is due to some other reason, e.g., trauma, capillary rupture, etc., but because one is on an anticoagulant it takes longer for the bleeding to stop.

- It is therefore imperative that the anticoagulant inhibits pathological thrombosis without interfering with physiological hemostasis.

- From an efficacy endpoint perspective, one should look at whether a new anticoagulant in AF prevents ischemic stroke since this is the stroke type caused by AF and can be prevented by the new anticoagulant; the new anticoagulant can’t prevent hemorrhagic stroke (a safety endpoint), which is anyway not caused by AF.

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**Conflict of Interest**

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**References**


