A Paradigm Shift: The New Novel Oral Anticoagulation Agents

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ABSTRACT

Atrial fibrillation (AF) is the most common arrhythmia and represents one-third of the arrhythmia-related hospital admissions in the developed countries. Embolic strokes associated with AF are more severe and disabling. Thromboembolic stroke prevention is a major goal in treatment of AF and Warfarin has successfully served this purpose for many years. Drug-drug interaction and regular monitoring with Warfarin pose a significant challenge where health care system has limited resources; and lack of a well-structured health system, hinders regular International Normalized Ratio (INR) monitoring. Novel oral anticoagulants (NOACs) have opened up a new exciting chapter in the field of anticoagulation in non-valvular atrial fibrillation (NVAF). This review discussed the landmark trials that led to the development of NOACs and explored the potentials of these new agents with simultaneous comparison of Warfarin.


INTRODUCTION

Atrial fibrillation (AF) remains a very important risk factor for ischemic stroke worldwide and more so in the developing countries where anticoagulation and follow-up is not as stringent as in the Europe and North America. Rheumatic valvular heart disease (RVHD) is much more common in Pakistan and India and makes up to 60 - 70% of AF incidence.1 The risk of thromboembolic stroke is five times greater in the presence of NVAF.2-5 Lack of large population-based studies and registries make it difficult to estimate total incidence of AF-related stroke in Pakistan and the Sub-continent. A small study from Karachi showed that non-rheumatic atrial fibrillation represented 3.8 % of ischemic strokes.6 Literature from India suggests that AF is a cause of 17 - 18% embolic strokes in RVHD.1 Most of the randomized control trials, which are taken from the composition of expert guidelines on atrial fibrillation, lack external validity, with underestimated representation of minorities and females.7

Although the risk of stroke in AF has been observed since 1960s,8 it was not until 1989 that the first trial proving the effectiveness of anticoagulation therapy in AF was published.9 Since then, the vitamin K antagonist (Warfarin) has been the mainstay of anticoagulation in AF. Anticoagulation reduces the frequency and severity of strokes in AF patients.10-12 Despite its effectiveness, Warfarin carries significant risk of bleeding,13 and interaction with several medications requires regular monitoring. In the most controlled randomized settings, patients taking Warfarin are shown to achieve therapeutic levels in only 62 - 66% at the best.14 Warfarin is the mainstay of anticoagulation for AF in Pakistan but lack of resources, patient follow-up, and education make INR monitoring difficult.1

Mechanism of action: Based on the mechanism of action, NOACs can be divided into two major classes. Direct thrombin inhibitor, i.e. Dabigatran and Factor Xa inhibitors, e.g. Apixaban, Endoxaban and Rivaroxaban. Warfarin indirectly inhibits the activation of clotting factor II, VII, IX and X as illustrate, in the schematic (Figure 1).15

Bleeding risk stratification for AF patients on anticoagulation: Annual risk of major bleeding with Warfarin is 1.4%.16 Several scoring systems are studied to stratify risk of bleeding. Most notables are HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly,17 (Table I), HEMMOR2HAGES,18 and ATRIA,16 which have been extensively validated in predicting bleeding in AF patients on anticoagulation.19

As of now, there is no longitudinal data on bleeding risk with NOACs, as there is no head-to-head comparison between NOACs and traditional anticoagulation
strategies. However, one can carefully imply patient's unchangeable risk factors into consideration before deciding the dose and type of NOACs.

In the last decade, research into finding a new oral anticoagulant has led to the development of several agents that have shown the potential to replace Warfarin. In this article, the authors review the currently available oral anticoagulant agents used in stroke prevention due to AF.

**Warfarin:** Effectiveness of Warfarin in stroke prevention in NVAF is well known. It has shown to be beneficial as both primary and secondary stroke prevention strategy. A meta-analysis of several primary and secondary prevention trials on Warfarin showed a 64% relative risk reduction in stroke (95% CI; 49%-74%). Warfarin inhibits an important enzyme epoxide reductase and decreases the synthesis of clotting factors II, VII, IX, and X and prolongs prothrombin time. Warfarin treatment faces many day-to-day challenges, on the part of both patient and physician. A recent study, comparing regular monthly INR testing in a clinic to weekly home testing, found that time in therapeutic range (TTR) were 62% and 66%, respectively. Thus concerning given patients are either over anticoagulated or inadequately anti coagulated one-third of the time; and therefore, are at risk of bleeding complications and stroke. One study showed physician's decision to prescribe Warfarin for NVAF is strongly driven by perceived risk of Warfarin-related bleeding rather potential benefit of stroke prevention. A review and meta-analysis of previously published studies conducted by Reynolds et al. found the incidence of stroke was 5.8 times higher than normal when the INR is 1.1-2.1, which is close to the risk in patients not on anticoagulation. It also showed that patients with and INR > 3.0 are three times more likely to experience bleeding complications.

Warfarin has several drug-drug and drug-food interactions. Warfarin undergoes hepatic metabolism with Cytochrome P450. All medications that inhibit or induce Cytochrome P450 will alter the INR. Several food classes including spinach, green tea, broccoli, lettuce, turnip, grapes, soya bean and green beans contain large amount of vitamin K and are well known to effect INR levels. Patients are advised to consume a consistent amount of these food items so that their Warfarin dose remains predictable. Given all these challenges associated with the use of Warfarin, the need for alternative oral anticoagulants becomes imperative.

**Ximelagatran:** The first oral direct thrombin inhibitor, Ximelagatran was studied in two large phase III, randomized trials for AF and secondary stroke prevention (SPORTIF III and V), and showed non-inferiority to Warfarin. Ximelagatran for the first time showed utility of direct thrombin inhibitors as a viable option for stroke prevention in AF and a possible alternative to Coumadin.

**Dabigatran:** The direct thrombin inhibitor Dabigatran Exetilate was the first oral anticoagulant to emerge as an effective alternative to Warfarin. Given though an oral route, Dabigatran Exetilate (prodrug) gets converted into its active form - Dabigatran. It reaches its peak plasma concentration within 2 hours, and competitively inhibits thrombin in a selective and reversible way. Eighty percent of the drug is renally excreted in an unchanged form. Unlike Warfarin, metabolism of Dabigatran is not affected by hepatic enzyme system P450, that means lesser drug-drug interactions and more reliable effect. The RE-LY trial is a large multi-center randomized non-inferiority designed trial. It compared two doses of Dabigatran (110 mg and 150 mg, twice daily) to adjusted-dose of Warfarin in patients with NVAF. RE-LY trial enrolled 50% Warfarin naïve patients. In Dabigatran 150 mg, there was equal distribution of patients considering their CHADs score (CHADS 0-1, 31%, 2, 35%, and > 2, 32%). In RE-LY trial time in therapeutic range (TTR) was 64%. Both doses were shown to be significantly better than adjusted-dose Warfarin.
non-inferior to Warfarin in regard to the primary outcome of stroke and systemic embolism. The 150mg dose was also shown to be superior to Warfarin (relative risk 0.66, 95% CI 0.53 to 0.82, p < 0.001). The risk of life-threatening bleeding associated with the two doses of Dabigatran (110 mg and 150 mg) was lower than that with Warfarin (p < 0.001 and 0.04, respectively). Risk of hemorrhagic stroke was also low in Dabigatran group (p < 0.001).30 Greatest benefit of stroke reduction was found in patients with previous TIA or stroke. Incidence of dyspepsia was seen in doses, 110 and 150 mg. However, the higher dose of Dabigatran (150 mg) caused more gastrointestinal hemorrhage than Warfarin. A subsequent analysis found the increased risk of gastrointestinal bleeding correlated significantly with increased age, suggesting the use of a lower dose of Dabigatran in patients over the age of 75 years.

Incidence of myocardial infarctions (MI) in the RE-LY trial is slightly higher in the Dabigatran group.30 This unexplained finding raised concerns about the drug's safety profile. However, further analysis of the trial showed this finding to be statistically non-significant.32 A recent analysis of pooled data of over 10,000 patients from 4 trials on the use of Dabigatran in venous thromboembolism prophylaxis in orthopedic surgery found no difference in acute coronary syndrome between Dabigatran and Enoxaparin.33 Post hoc analysis of RE-LY trial showed, patient treated with Dabigatran (both 110 and 150 mg doses) who underwent transthoracic echocardiogram pre-cardioversion did not show any significant increase in the incidence of left atrial (LA) thrombus when compared to Warfarin.34

In the United States, Food and Drug Authority (FDA) approved 150 mg and 75 mg Dabigatran doses. Lower dose is approved for creatinine clearance of 15 - 30 mL/minute. In the Europe, 110 mg is approved instead of 75 mg, along with 150 mg of Dabigatran.

**Rivaroxaban:** Rivaroxaban is a highly selective direct factor Xa inhibitor.35 It is rapidly absorbed after oral administration, with an estimated bioavailability of 80%, reaching its peak effect within 2-3 hours. Factor Xa inhibition by Rivaroxaban is dose-dependent, with a linear relationship between its plasma levels and prothrombin time.35 Two-thirds of the administered dose undergo hepatic metabolism, while the rest is renally excreted in the unchanged form.36 Therefore, Rivaroxaban's plasma level is increased and its action is potentiated by renal impairment.37 After being shown to be an effective anti coagulant in preventing venous thromboembolism following orthopedic surgery,38 its anticoagulant efficacy in AF patients was tested in the ROCKET-AF trial.39 ROCKET-AF was a phase III large randomized Warfarin-controlled, double blind, double dummy trial. After a mean follow-up period of 23.5 months, Rivaroxaban (20 mg daily for patients with normal renal function, 15 mg daily for patients with creatinine clearance 30 - 49 mL/minute) was found to be non-inferior to adjusted-dose of Warfarin (target INR 2.0 - 3.0) in preventing the study's primary outcome of ischemic stroke and systemic embolism. The population studied had a minimal CHADS2 score of 2 and a mean score of 3.48, higher than other studies of oral anticoagulants,30,39-42 TTR was only 55%. The annual rate of stroke or systemic embolism was 1.7% in the Rivaroxaban group and 2.2% in the Warfarin group (hazard ratio 0.79; 95% CI 0.66 to 0.96; p < 0.001 for non-inferiority). Although the primary safety outcome of major/non-major clinically relevant bleeding was similar in the two groups. Rivaroxaban was associated with lower risk of intracranial bleeding compared to Warfarin (0.5% vs. 0.7% per year; hazard ratio 0.67; 95% CI 0.47 to 0.93; p=0.02). On the other hand, major gastrointestinal bleeding was more common in the Rivaroxaban group.39

**Apixaban:** The second factor Xa inhibitor that was shown to be an effective alternate to Warfarin was Apixaban. It is rapidly absorbed in its active form, reaching its peak plasma level in 3 hours.43 One-fourth of the drug is excreted renally and 56% through the gastrointestinal route.44 Apixaban is metabolized in the liver by the enzyme CYP3A4/5.45 It should be used with caution in patients taking potent cytochrome P450 enzyme inhibitors like Ketoconazole, but is only minimally affected by less potent P450 inhibitors.45

The use of Apixaban for stroke prevention in AF patients was first evaluated in the AVERROES trial,41 a randomized trial comparing Apixaban to Aspirin in 5599 patients who were not eligible to Warfarin (either did not tolerate it previously or were expected not to tolerate it). The primary outcome of ischemic stroke occurred in 1.6% per year in the Apixaban group and 3.7% per year in the Aspirin group (hazard ratio with Apixaban 0.37, 95% CI 0.32 to 0.62; p < 0.001), with no difference in the incidence of major bleeding. Although promising, Apixaban superiority to Aspirin was not unexpected, given this was a population of patients at moderate risk for stroke (mean CHADS2 score 2.0). The head-to-head comparison of Apixaban to Warfarin came later in the ARISTOTLE trial,42 a randomized, double blind trial of Apixaban (5 mg twice daily) compared to adjusted-dose Warfarin (Target INR 2.0 - 3.0) in 18,201 patients with atrial fibrillation or flutter, and a CHADS2 score of at least 1 (mean 2.1) and TTR achieved was 62%. Stroke or systemic embolism - the study's primary outcome - occurred at a yearly rate of 1.27% with Apixaban and 1.6% with Warfarin (hazard ratio for Apixaban 0.79, 95% CI 0.66 to 0.95; p < 0.001 for non-inferiority and p=0.01 for superiority). Apixaban, compared to Warfarin was associated with significantly lower risk of major bleeding, including gastrointestinal bleedings (2.13% vs. 3.09%
Edoxaban is factor Xa inhibitor with 62% oral bioavailability. It achieves maximum concentrations within 1 to 2 hours and its elimination half-life is 8.75 to 10.4 hours. Approximately 50% of the absorbed drug is eliminated via kidney. In ENGAGE AF-TIMI 48 trial, two once-daily regimens of Edoxaban (60 mg and 30 mg) were compared with dose-adjusted Warfarin in patients with moderate-to-high-risk atrial fibrillation. The trial concluded that both once-daily regimens of Edoxaban were non-inferior to Warfarin for the prevention of stroke with a relative risk of 0.88 (CI, 0.75-1.03) Edoxaban 60 mg and [1.13 (CI, 0.97-1.31) Edoxaban 30 mg]. Both regimens were also associated with significantly lower rates of major bleeding as compared to dose-adjusted Warfarin with a relative risk of [0.80 (CI, 0.71-0.91) Edoxaban 60 mg] and [0.47 (CI, 0.41-0.55) Edoxaban 30 mg] and mortality from cardiovascular causes with a relative risk of [0.86 (CI, 0.77-0.97) Edoxaban 60 mg] and [0.85 (CI, 0.76-0.96) Edoxaban 30 mg].

The underuse of Warfarin: Amongst AF patients who are at moderate to high risk of stroke and are therefore candidates for prophylactic anticoagulation, less than one-half receive Warfarin, leaving a significant percentage of patients at high risk of stroke. Several reasons account for Warfarin's underuse, including patients' refusal due to the inconvenience of regular blood tests. The NOACs share several advantages over Warfarin. They are given in fixed doses, with no need for dose adjustments or monitoring of therapeutic levels, and no major interactions with drugs and food. These factors make them more convenient and may improve patients' compliance and willingness to take the medications.

Another important factor leading to underuse of Warfarin is physicians' reluctance to prescribe it, primarily due to the risk of bleeding. Warfarin is particularly under prescribed in elderly patients, in whom the risk of stroke is higher. All the three approved NOACs have lower incidence of fatal and intracranial bleeding compared to Warfarin, an important safety consideration. However, gastrointestinal bleeding was more frequent with Rivaroxaban and with the high dose of Dabigatran (150 mg twice daily) when used in patients older than 75 years, when compared to Warfarin.

Challenges:

A. Cost: Warfarin is available in an affordable generic form in most countries, making it an upfront cost-effective drug when initiation of therapy is being considered. However, Warfarin is the most common cause of hospitalization due to adverse drug events in patients of 65 years or older in the United States, accounting for one-third of such hospitalizations. The average cost of hospitalization resulting from Warfarin-related bleeding is $10819 in the US. The frequency, and therefore the cost, of these hospitalizations are offset by INR control in dedicated anticoagulation clinics, which despite increasing the cost of anticoagulation management, are believed to be cost-effective. The upfront costs of the three NOACs are considerably higher than Warfarin. A recent survey of 181 internists and cardiologists in San Francisco showed that cost is the most important factor that physicians consider when contemplating the use of Dabigatran. To date, there is no direct cost-effectiveness in comparison of NOACs with Warfarin. However, since Dabigatran was the first of the three agents to be approved and incorporated into several guidelines, the cost-effectiveness of Dabigatran was evaluated in several countries.

NOACs will be more expensive than Warfarin, but we have to take into account other factors (INR monitoring, stroke burden, and major bleeding) when looking at cost-effectiveness. Using data, derived from the RE-LY trial, these studies have shown that Dabigatran is cost-effective when the anticipated savings from differences in clinical outcomes (incidence of stroke and bleeding events) are taken into consideration. Definite conclusions regarding the cost-effectiveness of the NOACs will only be possible with further studies designed to specifically answer this question.

B. Renal impairment: Renal impairment represents a unique challenge in patients with AF. Chronic kidney disease (CKD) is an independent risk factor for thromboembolism in patients with atrial fibrillation. The increase in the incidence of thromboembolism is directly proportional to the decrease in eGFR and is further increased when associated with proteinuria. Conversely, CKD is also an independent risk factor for bleeding in patients anticoagulated with Warfarin, making it imperative that anticoagulation strategies in patients with severe kidney disease be individualized on a case-to-case basis.

All the three NOACs are at least partially renally excreted and their plasma concentration is expected to increase in cases of renal impairment. The pivotal trials examining the role of these agents in thromboprophylaxis of AF patients excluded individuals with severe renal impairment (Creatinine clearance (CrCl) < 30 ml/minute in RE-LY, and ROCKE-ROCKET-AF trials.
CrCl < 25 ml/minute in ARISTOTLE).42 Patients with moderate renal impairment were included in these trials, but with lower dose of the agent in ROCKET-AF and ARISTOTLE. The doses of Dabigatran in the RE-LY trial were not adjusted for patients with moderate renal impairment (CrCl 30 - 49 ml/minute), who constituted 19% of the study population. However, given the risk of extra cranial bleeding in patients over the age of 75 years was higher with Dabigatran compared to Warfarin, the FDA has recommended the use of the 75 mg dose in patients with CrCl ≥ 15 and < 30 ml/minute. FDA recommends avoiding Dabigatran use in patients with

Table II: Comparison of four landmark clinical trials on NOACs.

<table>
<thead>
<tr>
<th>Study</th>
<th>RELY (Dabigatran)</th>
<th>ROCKET-AF (Rivaroxaban)</th>
<th>ARISTOTLE (Apixaban)</th>
<th>ENGAGE AF-TIMI 48 (Edoxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>18,113</td>
<td>14,264</td>
<td>18,204</td>
<td>21,105</td>
</tr>
<tr>
<td>Study design</td>
<td>Randomized, open label, dabigatran dose blinded, warfarin parallel, non-inferiority study</td>
<td>Randomized, double-blind, double dummy, warfarin parallel- arm, event driven, non-inferiority study</td>
<td>Randomized, double-blind, double dummy, warfarin parallel- arm, non-inferiority study</td>
<td>Randomized, double-blind, double dummy, warfarin parallel- arm, non-inferiority study</td>
</tr>
<tr>
<td>Age, mean</td>
<td>71.5 years</td>
<td>73 years</td>
<td>70 years</td>
<td>72 years</td>
</tr>
<tr>
<td>CHADS2 Score (mean±SD)</td>
<td>2.1±1.1</td>
<td>3.48±1.9</td>
<td>2.1±1.1</td>
<td>2.8±0.9</td>
</tr>
<tr>
<td>Prior stroke (%)</td>
<td>20.3</td>
<td>54.9</td>
<td>19.2</td>
<td>28</td>
</tr>
<tr>
<td>Male</td>
<td>63.6%</td>
<td>61.3%</td>
<td>64.5%</td>
<td>62%</td>
</tr>
<tr>
<td>Previous VKA use (%)</td>
<td>50</td>
<td>62</td>
<td>57</td>
<td>59</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>2 years</td>
<td>1.9 years</td>
<td>1.8 years</td>
<td>2.8 years</td>
</tr>
<tr>
<td>Treatment arm</td>
<td>a) 150 mg twice daily</td>
<td>a) 20 mg once daily</td>
<td>a) 5 mg once daily</td>
<td>a) 60 mg once daily</td>
</tr>
<tr>
<td></td>
<td>b) 110 mg twice daily</td>
<td>b) 15 mg once daily#</td>
<td>b) 2.5 mg twice daily</td>
<td>b) 30 mg once daily*</td>
</tr>
<tr>
<td>Control arm</td>
<td>Warfarin (INR 2-3)</td>
<td>Warfarin (INR 2-3)</td>
<td>Warfarin (INR 2-3)</td>
<td>Warfarin (INR 2-3)</td>
</tr>
<tr>
<td>Mean TTR</td>
<td>64</td>
<td>55</td>
<td>62</td>
<td>65</td>
</tr>
<tr>
<td>Primary efficacy end-point</td>
<td>Stroke or thromboembolism (ITT)</td>
<td>Stroke or thromboembolism (PP)</td>
<td>Stroke or thromboembolism (ITT)</td>
<td>Stroke or thromboembolism (ITT)</td>
</tr>
<tr>
<td>Stroke or systemic embolism</td>
<td>1.54% dabigatran 110mg</td>
<td>1.11% dabigatran 150mg*</td>
<td>1.171 warfarin</td>
<td>2.2% warfarin</td>
</tr>
<tr>
<td></td>
<td>1.71% warfarin</td>
<td>1.71% warfarin</td>
<td>1.71% warfarin</td>
<td>1.71% warfarin</td>
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<tr>
<td>Stroke</td>
<td>1.01% dabigatran 150mg</td>
<td>1.44% dabigatran 110mg</td>
<td>1.57% warfarin</td>
<td>1.57% warfarin</td>
</tr>
<tr>
<td></td>
<td>1.65% rivaroxaban*</td>
<td>1.96% warfarin</td>
<td>1.51% warfarin</td>
<td>1.51% warfarin</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.10% dabigatran 150mg*</td>
<td>0.12% dabigatran 110mg*</td>
<td>0.38% warfarin</td>
<td>0.26% warfarin</td>
</tr>
<tr>
<td></td>
<td>0.26% rivaroxaban*</td>
<td>0.44% warfarin</td>
<td>0.47% warfarin</td>
<td>0.47% warfarin</td>
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<tr>
<td>Ischemic stroke</td>
<td>0.93% dabigatran 150mg*</td>
<td>1.34 dabigatran 110mg</td>
<td>1.22 warfarin</td>
<td>0.97% warfarin</td>
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<tr>
<td>Major bleeding</td>
<td>2.87% dabigatran*</td>
<td>3.32% dabigatran 150mg</td>
<td>3.4% warfarin</td>
<td>2.13% warfarin</td>
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<tr>
<td></td>
<td>3.6% rivaroxaban*</td>
<td>3.4% warfarin</td>
<td>3.09% warfarin</td>
<td>2.75% warfarin</td>
</tr>
<tr>
<td>Intra-atrial bleeding</td>
<td>0.3% dabigatran 150mg*</td>
<td>0.23% dabigatran 110mg*</td>
<td>0.74% warfarin</td>
<td>0.5% rivaroxaban*</td>
</tr>
<tr>
<td></td>
<td>0.5% rivaroxaban*</td>
<td>0.7% warfarin</td>
<td>0.80% warfarin</td>
<td>0.33% rivaroxaban*</td>
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<tr>
<td>GI bleed</td>
<td>1.51% dabigatran 150mg*</td>
<td>1.12% dabigatran 110mg*</td>
<td>1.02% warfarin</td>
<td>3.2% warfarin</td>
</tr>
<tr>
<td></td>
<td>3.2% rivaroxaban*</td>
<td>2.2% warfarin</td>
<td>0.86% warfarin</td>
<td>0.76% apixaban</td>
</tr>
<tr>
<td>Primary route of elimination/ or thromboembolism</td>
<td>Renal excretion (80%)</td>
<td>Hepatic excretion (66%)</td>
<td>Hepatic excretion (65%)</td>
<td>Hepatic excretion (75%)</td>
</tr>
</tbody>
</table>
| NOAC, Novel Oral AntiCoagulant; RELY, Randomized Evaluation of Long-term anticoagulant therapy; ROCKET-AF, Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonist for prevention of stroke and Embolism Trial in Atrial Fibrillation; ARISTOTLE, Apixaban for Reduction In Stroke and other Thromboembolic Events in atrial fibrillation; ENGAGE AF-TIMI 48, Effective AntiCoagulation with factor Xa next Generation in Atrial Fibrillation Event rate for RE-LY, ARISTOTLE, and ENGAGE AF was %/year, however for ROCKET AF, number/100 patient year. * P < 0.05 ^ Superiority; # In patients with eGFR 30 - 49ml/min; µ In patients with two or more of the following criteria: age≥80, body weight <60 kg, or serum creatinine ≥1.5 mg/dL ∆ 50%-reduced dose is used in patients with CrCl 30-50 mL/min, body weight <60 kg, or concomitant use of verapamil, quinidine or dronedarone at randomization or during study. TTR = Time in therapeutic range (for warfarin therapy); ITT = Intention to treat; PP = Per protocol.

Table III: Comparison of Warfarin to NOACs.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability(%)</td>
<td>98</td>
<td>6-7</td>
<td>63-79</td>
<td>66</td>
<td>50</td>
</tr>
<tr>
<td>T1/2(hours)</td>
<td>20-60</td>
<td>7-17</td>
<td>7-13</td>
<td>8-15</td>
<td>9-11</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>99</td>
<td>35</td>
<td>95</td>
<td>87</td>
<td>54</td>
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<tr>
<td>Dosing</td>
<td>Once a day</td>
<td>Twice a day</td>
<td>Once a day</td>
<td>Twice a day</td>
<td>Once a day</td>
</tr>
<tr>
<td>Metabolism/Elimination</td>
<td>Liver 100%</td>
<td>Renal 80%</td>
<td>Liver 70%</td>
<td>Renal 30%</td>
<td>Renal 25%</td>
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<td>Substrate CYP</td>
<td>2C9, 3A4</td>
<td>No</td>
<td>3A4, 2J2</td>
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<td>3A4</td>
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<tr>
<td>Food interaction</td>
<td>Yes</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Monitoring</td>
<td>INR</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Target</td>
<td>II, VIII, IX, X, protein S and C</td>
<td>II</td>
<td>Xa</td>
<td>Xa</td>
<td>Xa</td>
</tr>
</tbody>
</table>

CrCl < 15 ml/minute, with a box label warning. The safety of Dabigatran at 75 mg in this group of patients (with CrCl ≥ 15 and < 30 ml/minute) has not been studied and should therefore be used with caution. FDA allows using decreased dose of 15 mg once a day of Rivaroxaban in patients with CrCl ≥ 15 and ≥ 30 ml/min. Apixaban is approved with 2.5 mg twice a day for patients with serum creatinine ≥ 1.5 mg/dL. Until further data regarding the use of NOACs in patients with severe renal impairment is available, Warfarin will remain the drug of choice in this patient population.

C: The quest to find an antidote: The major limitation of the NOACs is their lack of effective antidote. Management of major bleeding in patients on the new agents is, therefore, challenging. Several approaches have been considered and/or tested. Plasma transfusion, although rich in coagulation factors, does not reverse anticoagulation caused by factor inhibition and would only be beneficial in the presence of dilutional coagulopathy. Studies into the efficacy of prothrombin complex concentrate (PCC) as an antidote for Dabigatran showed favourable results in some but not other animal studies. The use of PCC was also evaluated in a human ex-vivo study and was found to be ineffective in reversing Dabigatran's effect. The same study showed recombinant factor VIIa (rFVIIa) to have some efficacy in reversing Dabigatran's action, a finding supported by an experience with postoperative Dabigatran-related bleeding. PCC and rFVIIa improved coagulation parameters and some clinical parameters caused by Rivaroxaban in a rabbit model, and a human ex-vivo model - where rFVIIa was more effective than PCC. Researches into agents that may help reverse Apixaban's action are also ongoing, and an in-vitro study using PCC and rFVIIa yielded promising early results.

There is an ongoing Phase-2 clinical trial of experimental agent PER977 that binds to Dabigatran, Rivaroxaban, Apixaban and Edoxaban through non-covalent hydrogen binding and charge-charge interactions. In animal study, 300-300 mg dose of PER977 reverses the Edoxaban anticoagulant effect within 10-30 minutes and this effect was sustained for 24 hours.

In a recent study Idarucizumab, a monoclonal antibody fragment, has shown the reversal of Dabigatran anticoagulant effect in 88 to 98% of patients within minutes. This is a very important milestone towards the search of an antidote. When a patient on Dabigatran have major bleeding event or needs an urgent surgery, an antidote like Idarucizumab that reverses the anticoagulant effect rapidly and completely, will be of great importance.

For life-threatening bleeding, secondary to Dabigatran, hemodialysis and hemofiltration could be employed, as Dabigatran is dialyzable due to its poor plasma protein binding. Rivaroxaban is tightly protein-bound and therefore dialysis is not suitable. Best test to detect the presence of Dabigatran in the system is thrombin time (> 3 ng/ml). If thrombin time is normal, Dabigatran is not present. In some cases anti Xa, anti-factor Xa assay can be used, aPTT test is unreliable for any of the NOACs and often deranged.

All of the above mentioned studies are in experimental and in preliminary phases. Studies to validate the clinical use and safety of these measures are important before they can be used in clinical practice. In the mean time, management of patients that present with major bleeding, associated with the NOACs, should target the cessation of source of bleeding, discontinuation of the drug and supportive blood product transfusion. PCC (25 U/kg, repeat if needed) and rFVIIa can be used as an antidote for Dabigatran, while PCC (25 U/kg, repeat if needed), rFVIIa or FEIBA can be used in case of antiXa inhibitors. Still there is no large scale trial conducted to evaluate the efficacy of these antidotes.

Oral anticoagulant of choice: All four NOACs are comparable to Warfarin in several characteristics including convenience, and lower risk of fatal / intracranial hemorrhage. They also share similar disadvantages of high cost and need for caution in renal diseases. The main advantage of Warfarin over these NOACs is availability of anti dote in the form of Vitamin K and FFP, but this advantage is offset by a complicated dosing regimen and vigorous INR monitoring which is only achieved in 62 - 66% of cases at best, in well set healthcare systems of the Europe and North America; but incidence of achieving therapeutic INR will be much lower in India and Pakistan, due to lack of awareness and limited resources.

Nonetheless, three meta-analyses comparing the NOACs were performed, based on the RE-LY, ROCKET-AF and ARISTOTLE. All three meta-analyses found Apixaban to have caused less major bleeding. The analysis by Schneeweiss et al. also found that in patients with CHADS2 score ≥ 3, Apixaban and Dabigatran were non-statistically superior to Rivaroxaban in protecting from ischemic stroke and systemic embolism. Testa et al. found that Rivaroxaban caused less systemic embolism than Apixaban and Dabigatran, and that Dabigatran was associated with less hemorrhagic stroke than Rivaroxaban. They also concluded that Dabigatran was associated with more myocardial infarctions compared to the other two agents. On the other hand, Mantha et al. found all three agents had similar efficacy. It is important, though, to view these conclusions in the context of well-established limitations of indirect meta-analysis, including significant inconsistency when compared to direct meta-analyses, and these inconsistencies are more commonly seen when only a few trials are included. Banerjee et al. compared the net clinical benefit of the three NOACs in a model, based on the Danish National Patient Registry.
The aim of the study was to compare the three NOACs in a “real world” cohort. The relative risks of ischemic stroke and intracranial hemorrhage in the registry population were estimated, based on data from RE-LY, ROCKET-AF, and ARISTOTLE. The analysis concluded that for patients with CHADS2 score ≥ 2, Dabigatran [150 mg BID dose] was associated with the lowest rate of ischemic stroke per 100 persons years and lowest number needed to treat (1.09,52) compared to Apixaban (1.30,59), Rivaroxaban (1.45,60), Dabigatran [110 mg BID dose] (1.50,66) and Warfarin (1.65,74), respectively. It also showed that Dabigatran [110 mg BID dose] had the lowest rate of intracranial hemorrhage per 100 persons years (0.14) compared to Dabigatran [150 mg BID dose, 0.17], Apixaban (0.18), and Rivaroxaban (0.29).84

CONCLUSION

NOACs are potential alternative in the AF stroke prevention. Health care system in Pakistan faces continuous challenges which include limited health resources, lack of patient education and follow-up, financial difficulties making regular INR monitoring less practical for most of the patients, specially in rural areas. Although cost will be a major deciding factor in our health care system, but NOACs may be cost-effective.

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