Current Perspective on Use of NOAC in Clinical Practice in India

Jamshed J Dalal¹, Anil Dhall², Abhay Bhave³

Abstract
Oral vitamin K antagonists (VKA) such as warfarin have been the mainstay of therapy for stroke prevention in patients with non valvular atrial fibrillation (NVAF) while low-molecular-weight heparin, fondaparinux and adjusted-dose warfarin or aspirin have been routinely used for thromboembolism (VTE) prophylaxis in patients undergoing total hip or knee replacement. However, VKAs are associated with considerable limitations, including increased risk of bleeding and narrow therapeutic window. Novel oral anticoagulants (NOACs, now referred as Non Vit K dependent oral anticoagulants), including the direct thrombin inhibitor dabigatran and direct Factor Xa inhibitors such as rivaroxaban and apixaban are now approved alternatives to warfarin for prophylaxis of stroke and systemic embolic events (SEE) in patients with NVAF and treatment and prophylaxis of VTE. The efficacy and safety of NOACs have been proven in several clinical trials. The advantages offered by NOACs such as rapid onset and termination of action, predictable anticoagulant effect, less frequent laboratory monitoring make them promising alternatives to warfarin. However, clinicians in India seek more information over the practical aspects that require due consideration to ensure proper use of these drugs. The article addresses some crucial aspects of NOAC therapy such as measurement of anticoagulant effects, transition between different agents, ensuring drug intake compliance, dealing with dosing errors, management of bleeding complications etc based on the guidance offered by the European Heart Rhythm Association in 2013.

Introduction
Until recently, Vitamin K antagonists (VKAs) such as warfarin were the only approved oral anticoagulants for treatment of non valvular atrial fibrillation (NVAF). Similarly, low-molecular-weight heparin (LMWH), fondaparinux, low-dose unfractionated heparin (LDUH), adjusted-dose warfarin or aspirin constituted the standard venous thromboembolism (VTE) prophylaxis in patients undergoing total hip or knee replacement (THR or TKR). Unfortunately, thromboprophylaxis with VKAs have considerable limitations, including increased risk of bleeding, narrow therapeutic window and individualized dosing based on the international normalized ratio (INR). Other limitations include delayed onset of action necessitating a bridging therapy with heparin initially, genetic heterogeneity in pharmacokinetic response and food as well as drug interactions. Since 2007, three novel oral anticoagulation agents (NOACs, now referred as Non Vit K dependent oral anticoagulants) (dabigatran, rivaroxaban, apixaban) have been approved as alternatives to warfarin for prophylaxis of stroke and systemic embolic events (SEE) in patients with nonvalvular atrial fibrillation (NVAF) and treatment and prophylaxis of VTE. Several clinical trials have proved these agents as safe and efficacious. In addition they have added advantages such as rapid onset and termination of action, predictable anticoagulant effect such that routine laboratory monitoring is not required.

This article is an attempt to highlight the current perspective of NOAC use in NVAF and prevention of other thromboembolic events in deep vein thrombosis, and secondary prevention of stroke especially with an Indian perspective.

Novel Oral Anticoagulants - An Overview
Dabigatran an oral direct thrombin inhibitor (DTI), was the first NOAC to gain approval for stroke prevention in atrial fibrillation (SPAF) in the United States; rivaroxaban and apixaban, direct factor Xa (FXa) inhibitors followed dabigatran. Thrombin as the final effector...
Table 1: NOACs - pharmacology, drug interactions and dosage regimen

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
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<tbody>
<tr>
<td><strong>Pharmacology</strong></td>
<td></td>
<td></td>
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<tr>
<td>Mechanism of action</td>
<td>Selective direct thrombin inhibitor</td>
<td>Selective direct FXa inhibitor</td>
<td>Selective direct FXa inhibitor</td>
</tr>
<tr>
<td>Oral bioavailability %</td>
<td>6</td>
<td>80–100</td>
<td>50</td>
</tr>
<tr>
<td>Protein Binding %</td>
<td>35</td>
<td>95</td>
<td>87</td>
</tr>
<tr>
<td>T max</td>
<td>0.5–2 h</td>
<td>1 to 4 h</td>
<td>1 to 4 h</td>
</tr>
<tr>
<td>Half-life</td>
<td>12 to 17 h</td>
<td>5 to 13 h</td>
<td>8 to 15 h</td>
</tr>
<tr>
<td>Renal elimination</td>
<td>85%</td>
<td>66 (36 unchanged and 30 inactive metabolites)</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food effect</td>
<td>Delays absorption</td>
<td>Delays absorption</td>
<td>Not reported</td>
</tr>
<tr>
<td>Effect of age</td>
<td>None</td>
<td>Variable</td>
<td>Not reported</td>
</tr>
<tr>
<td>Effect of body weight</td>
<td>None</td>
<td>None</td>
<td>Not reported</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Yes; verapamil, reduce dose; dronedarone: avoid; Potent inducers of P-gp*: avoid</td>
<td>Yes; potent inhibitors of CYP3A4 and P-gp*: avoid; Potent inducers of CYP3A4‡ and P-gp† use with caution</td>
<td></td>
</tr>
<tr>
<td>P-glycoprotein</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Means to monitor interaction</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Atrial fibrillation</td>
<td>Creatinine clearance (CrCl): ≥ 30 mL/min: 150 mg BID</td>
<td>CrCl: &gt; 50 mL/min: 20 mg QD</td>
<td>5 mg BID; 2.5 mg BID if any 2 of the following 3 are present: 1. age ≥ 80 y</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>CrCl &gt;30 mL/min: 150 mg orally, twice daily after 5-10 days of parenteral anticoagulation</td>
<td>15-29 mL/min: 75 mg BID</td>
<td>2. weight ≤ 60 kg, or 3. serum creatinine ≥1.5mg/dl Prophylaxis of DVT in THR/TKR: 2.5 mg BD (initial dose to be taken within 12 to 24 hours after surgery) for 35 and 12 days respectively Treatment of DVT and PE: 10mg BD X 7days fb 5mg BD [Zuccotti 2014] This is approved only in EU region in July 2014</td>
</tr>
</tbody>
</table>

†Potent inhibitors of CYP3A4 include antifungals (e.g., ketoconazole, itraconazole, voriconazole, posaconazole), chloramphenicol, clarithromycin, and protease inhibitors (e.g., ritonavir, atazanavir). P-gp inhibitors include verapamil, amiodarone, quinidine, and clarithromycin. P-gp inducers include rifampicin, carbamazepine, and phenytoin. ‡Potent CYP3A4 inducers include phenytoin, carbamazepine, and phenobarbital. CYP cytochrome P450 isoenzyme; F factor; P-gp P-glycoprotein.

Risk Stratification in AF

AF has substantial impact on mortality and morbidity mainly because of thromboembolic complications resulting in ischemic stroke. In India, there is paucity of data on AF, however, data from on-going Indian Heart Rhythm Society-AF registry and Indian cohorts of Randomized Evaluation of Long-term Anticoagulation Therapy [RE-LY] and Real-life global survey evaluating patients with atrial fibrillation [REALISE] studies indicate that average age of Indian AF patient is a decade earlier than in western world possibly because of rising frequency of co-morbidities such as hypertension and diabetes.3–5

Approximately 15% of strokes are associated with AF and the incidence increases with age.7 It is crucial to prevent thromboembolic events in AF. Antithrombotic strategies in AF include antiplatelet agents (aspirin), oral anticoagulants (OACs), notably VKAs (warfarin); recently, NOACs have been added to the armamentarium.1

Stroke risk is not uniform in AF and depends on other risk factors such as congestive heart failure, hypertension, age, diabetes mellitus, and prior stroke/transient ischemic attack, all of which are integrated in a widely used tool, CHADS2 score. Stroke risk increases with increasing CHADS2 scores (stroke rate: 2.0–4.5 with CHADS2 of 1-2 Vs 6–12 with CHADS2 of 4).5

CHA2DS2-VASc, an adaptation of CHADS2, incorporates additional risk factors: vascular disease, age 65–74 years, and female gender. The
Table 2: NOAC in NVAF – results from pivotal phase III trials

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Interventions</th>
<th>Patient baseline/characteristics</th>
<th>Efficacy results</th>
<th>Safety outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY:</td>
<td>Dabigatran etexilate 110 mg bid (blinded) or Dabigatran etexilate 150 mg bid (blinded) Vs Open-label warfarin (INR 2-3); n = 18,113</td>
<td>Age: 71 (mean) CHADS 2: 2.1 ± 1.1 (D110 mg, Warf); 2.2±1.2 (D150 mg) similar distribution of co-morbidities: Prior stroke/transient ischemic attack: 3623 Hypertension: 14283 Diabetes: 4221</td>
<td>Composite of stroke and SE: D110 mg vs. Warf: RR 0.91 (95% CI: 0.74–1.11); P value (non-inferiority) &lt;0.001 D150 mg vs. Warf: RR 0.66 (95% CI: 0.53–0.82); P value (superiority)&lt; 0.001; RR 0.65 (95% CI: 0.52–0.81); P value (superiority)&lt; 0.001 MI events: D110 mg vs. Warf: RR: 1.35 (0.98–1.87) p-value = 0.07; D150 mg vs. Warf: RR: 1.38 (1.00–1.91) p-value =0.048 All-cause mortality: D110 mg vs. Warf: RR: 0.91 (0.80–1.03) p-value =0.13; D150 mg vs. Warf: RR: 0.88 (0.77–1.00) p-value =0.051</td>
<td>Major and non-major clinically relevant bleeding*: 14.9% &amp; 14.5% per year in rivaroxaban and warfarin respectively; HR, 1.03; 95% CI, 0.96 to 1.11; P = 0.44</td>
</tr>
<tr>
<td>Rocket-AF:</td>
<td>Rivaroxaban 20mg or 15mg (in patients with creatinine clearance of 30-49ml/min) once daily vs Warfarin dose-adjusted to INR 2-3; once daily, n=14 264</td>
<td>Age: 73 (median) CHADS2: 3.48±0.94 and 3.46±0.95 in rivaroxaban and warfarin respectively. Similar distribution of co-morbidities: Prior stroke/transient ischemic attack: 7811 Hypertension: 12910 Diabetes: 5695</td>
<td>Composite of stroke and SE: 1.7% vs 2.2% in rivaroxaban and warfarin groups per year; HR 0.79 (95% CI: 0.66-0.96); P&lt;0.001 MI events 0.9% and 1.1% per year in rivaroxaban and warfarin respectively; HR in the rivaroxaban group, 0.81; 95% CI (0.63 to 1.06) P = 0.12 All-cause mortality: 1.9% and 2.2% per year respectively, HR: 0.85; 95% CI(0.70 to 1.02) P = 0.07</td>
<td>Major and non-major clinically relevant bleeding*: 14.9% &amp; 14.5% per year in rivaroxaban and warfarin respectively; HR, 1.03; 95% CI, 0.96 to 1.11; P = 0.44</td>
</tr>
<tr>
<td>Aristotle-</td>
<td>Apixaban (5 mg bid or 2.5 mg bid for pts with creatinine clearance ≤60 ml/min) once daily vs Double-blind warfarin (INR 2-3); n = 18 201</td>
<td>Age: 70 (median) CHADS2: 2.1 ± 1.1 (mean ± SD) Similar distribution of co-morbidities: Prior stroke/transient ischemic attack: 3538 Hypertension: 15916 Diabetes: 4547</td>
<td>Composite of stroke and SE: 1.27% vs 1.60% in apixaban and warfarin Groups per year; HR with apixaban, 0.79; 95% CI (0.66 to 0.95); P&lt;0.001 for noninferiority; P=0.01 for superiority MI events: 0.53 vs 0.61 in apixaban and warfarin respectively HR: 0.88 (0.66-1.17) p-value: 0.37 All-cause mortality: 3.52% vs 3.94% in apixaban and warfarin respectively HR: 0.89; 95% CI (0.80 to 0.98; P = 0.047).</td>
<td>Major and non-major clinically relevant bleeding*: 14.9% &amp; 14.5% per year in rivaroxaban and warfarin respectively; HR, 1.03; 95% CI, 0.96 to 1.11; P = 0.44</td>
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</table>

 European Society of Cardiology (ESC) 2010 guidelines recommend OACs for patients with a CHADS2 score ≥2; patients with a CHADS2 score < 2 should be assessed using CHA2DS2-VASc. Those with a CHA2DS2-VASc score of 1 may receive OAC (preferred) or aspirin, and patients with a CHA2DS2-VASc score of 0 may receive aspirin or no antithrombotic therapy (preferred as the risk of bleeding may exceed benefit). Direct comparison of VKA and aspirin in nine studies demonstrated VKAs to be superior to aspirin with a relative risk (RR) reduction of 39%. Hart et al, in their meta-analysis, reported dose-adjusted warfarin as more efficacious than aspirin (64% vs 20%) in reducing stroke in AF.10

**VKA Use in India**

VKAs are used hesitantly in AF patients because of their limitations. Successful anticoagulation with VKAs entails the need for frequent dose adjustment and INR monitoring; INR 2.0–3.0 helps balance between prevention of ischemic stroke and avoidance of bleeding complications. However, many places in India lack laboratories with standardized measurement of prothrombin time (PT)/INR. In a retrospective Indian study, overall anticoagulant control was generally poor with many patients in a state of undertreatment and INRs recorded, only 17.8% were in the therapeutic range). Another Indian study showed that the knowledge base of clinicians regarding OAC management was unsatisfactory with a tendency to under-dose patients due to fear of bleeding. Indians with their different dietary habits are more prone for warfarin-
food interactions. Green leafy vegetables, cabbage, cauliflower, and other foods rich with vitamin K in the Indian diet cause lability in INR values. Over the counter medications such as nonsteroidal anti-inflammatory drugs, herbal foods (e.g. garlic, fenugreek) and use of concomitant antituberculous drugs (isoniazid or rifampicin) may also alter INR values and result in under or over anticoagulation.13

NOACs with their predictable pharmacokinetics and anticoagulant effects preclude the need for routine laboratory monitoring. Compared with warfarin, they have lower risk of intracranial bleeding, fewer food and drug interactions.14,9

**NOACs in AF - Clinical Trial Results**

NOACs have been compared with warfarin for SPAF in several randomized, clinical trials (RCTs).

Three large-scale randomized NOAC trials, RE-LY (dabigatran, D110 mg BD or D150 mg BD), Rivaroxaban Once-daily oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in AF (ROCKET-AF) and Apixaban for Reduction In Stroke and Other Thromboembolic Events in AF (ARISTOTLE) trial (apixaban, 5 mg BD) have shown that NOACs are therapeutically superior to warfarin (dabigatran 150 mg bid, apixaban), or at least non-inferior with a similar rate of hemorrhage (rivaroxaban) or a lower rate of hemorrhage (dabigatran 110 mg bid, apixaban). The results of these trials are described in detail in Table 2.15-17

The rates of intracranial hemorrhage (ICH) with both doses of dabigatran were less than warfarin; possible reasons could be decreased anticoagulation effect variability due to twice-daily dosing regimen. In addition, dabigatran selectively inhibits thrombin resulting in lesser bleeding as compared to warfarin which inhibits factors II, VII, IX, and X and proteins C and S.15 Based on RE-LY trial results, U.S Food and Drug Administration (FDA) has approved dabigatran 150 mg dose (75 mg in severe renal impairment), the European Medical Agency (EMA) has approved both 150 mg and 110 mg doses. In ROCKET-AF, there were no significant differences in rates of major bleeding between study drugs though ICH and fatal bleeding occurred less frequently in the rivaroxaban group. Apixaban was associated with lower rates of major bleeding, ICH and hemorrhagic stroke.

There are no ‘head to head’ trials comparing the three approved NOACs. Apixaban has demonstrated superiority over warfarin in all three major outcomes (stroke/SEE prevention, reduction in major bleeding and all-cause mortality). In addition, apixaban had similar rates of gastrointestinal (GI) bleeding as warfarin while dabigatran and rivaroxaban were associated with higher rates. Dabigatran was associated with higher rates of myocardial infarction where as rivaroxaban and apixaban had numerically significant lower rates.15-17

**VTE Treatment and Prophylaxis**

The exact incidence of VTE in the Indian population is not known because of non uniform reporting of such incidents; one prospective study in subjects undergoing major orthopedic surgery such as TKR, THR and proximal femur fracture fixation (PFF) without any prophylaxis reports the overall incidence of VTE and pulmonary embolism (PE) to be 6.12% and 0.6% respectively.18-20

There is a sub-optimal utilization of thromboprophylaxis in India. Two important reasons are underestimation of VTE incidence in India and fear of bleeding complication. Studies on patients hospitalized for medical illnesses with RR for development of DVT have observed much lower absolute risk for DVT and VTE compared to Western countries.21 Considering the significant morbidity, potential mortality and health care burden associated with VTE, risk assessment and appropriate thromboprophylaxis in targeted individual are crucial. Further, maintaining balance between benefit of VTE reduction and bleeding risk is a real challenge. Warfarin represents the only OAC that is licensed for long-term use but is further associated with numerous limitations as mentioned above. NOACs with its potential to address some of these limitations may simplify treatment strategies, encourage compliance with therapy and may reduce the economic burden of VTE. Several evidence-based guidelines22,23 for VTE prevention have provided recommendations including choice of thromboprophylaxis, timing of commencement, and duration of therapy. While the American College of Chest Physicians (ACCP) guideline has preference for LMWH amongst all anticoagulants, American Academy of Orthopedic Surgeons (AAOS) guideline does not recommend any specific anticoagulant for VTE prophylaxis in patients undergoing TKR or THR. The ACCP has suggested NOACs as an alternative to LMWH for patients with TKR or THR but does not consider these for patients with HFS. The ACCP has recommended starting LMWH either 12 hours or more preoperatively or 12 hours or more postoperatively and extending the thromboprophylaxis in the outpatient period for up to 35 days irrespective of the therapy used. Dual approach with mechanical [intermittent pneumatic compression device (IPCD)] and pharmaceutical combinations is preferred to maximize efficacy of thromboprophylaxis with minimum bleeding risk. Extended-duration thromboprophylaxis is also advised
Table 3: VTE treatment: clinical trial evidence

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Drug vs comparator</th>
<th>Efficacy results: recurrent VTE (HR)</th>
<th>Safety results (HR)</th>
<th>Major bleeding</th>
<th>Major / CRNM bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-Cover I – Dabigatran – DB²⁴</td>
<td>Dabigatran, 150 mg BID x 6 months vs Warfarin, INR 2-3 (TTR 59.9%) x 6 months</td>
<td>1.10 [P value: &lt;0.001 (NI)]</td>
<td>0.82 [P value: 0.38]</td>
<td>0.63 [P value: 0.002]</td>
<td></td>
</tr>
<tr>
<td>Re-Cover II– Dabigatran – DB²⁴</td>
<td>Dabigatran, 150 mg BID x 6 months vs Warfarin, INR 2-3 (TTR 59.9%) x 6 months</td>
<td>1.08 [P value: &lt;0.001(NI)]</td>
<td>0.69 [P value: 0.26]</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Einstein – DVT³⁶</td>
<td>Rivaroxaban, 15 mg BID x 3 weeks, then 20 mg QD x 3, 6, 12 months vs Enox 1 mg/kg BID ≥5 d, then warfarin, INR 2-3 (TTR=57.7%) x 3, 6, 12 months</td>
<td>0.68 [P value: &lt;0.001(NI)]</td>
<td>0.65 [P value: 0.21]</td>
<td>0.97 [P value: 0.77]</td>
<td></td>
</tr>
<tr>
<td>Einstein – PE³⁶</td>
<td>Rivaroxaban, 15 mg BID x 3 weeks, then 20 mg QD x 3, 6, 12 months vs Enox 1 mg/kg BID ≥5 d, then warfarin, INR 2-3 (TTR=62.7%) x 3, 6, 12 months</td>
<td>1.12 [P value: 0.003(NI)]</td>
<td>0.49 [P value: 0.003(sup)]</td>
<td>0.9 [P value: 0.23]</td>
<td></td>
</tr>
<tr>
<td>Amplify⁴⁷</td>
<td>Apixaban, 10 mg BID x 7 d, then 5 mg BID x 6 months vs Enox 1 mg/kg BID ≥5 d, then warfarin, INR 2-3 x 6 months (TTR 61%)</td>
<td>0.84 [P value: &lt;0.0001(NI)]</td>
<td>0.31 [P value: &lt;0.0001(sup)]</td>
<td>0.44 [P value: &lt;0.0001]</td>
<td></td>
</tr>
</tbody>
</table>

'Major primary outcome

in high-risk medical patients without any recommendation on optimal duration.²⁴ Western Australian Therapeutic Advisory group (WATAG) advocates thromboprophylaxis duration of 30 days for THR and 15 days for TKR.²⁵

Extensive clinical trials with three NOACs have been performed to examine their efficacy in patients undergoing major orthopedic surgery for thromboprophylaxis or for VTE treatment. These studies have been described in Table 3 and 4. Studies performed in acute VTE treatment have revealed that NOACs are as effective as LMWH and/or VKAs in reducing recurrent VTE; additionally, apixaban was superior to LMWH in reducing major bleeding episodes. Though there are no head to head studies analysing direct comparison of the different NOACs, trial data indicates favorable response to factor Xa inhibitors with rivaroxaban and apixaban performing better than dabigatran in reducing recurrent VTE and apixaban showing better safety profile amongst them. In the extension phase studies of NOACs with continued long-term therapy of 6 to 12 months, all NOACs have demonstrated superiority over no prophylaxis with comparable safety. Though, constrained with limitations relating to patient population (limited inclusion of elderly patients, patients with renal impairment, very obese patients and patients from non-white ethnic groups) and study design (little information on possible drug interactions), the promising results of these clinical studies have recognized NOACs as landmark advancement in anticoagulant care.²⁶

In the phase III studies that involved thromboprophylaxis with NOAC after major orthopedic surgery, factor Xa inhibitors showed superiority against enoxaparin [except one study (ADVANCE-1) with apixaban; did not meet the pre-specified statistical criteria for noninferiority] whereas direct thrombin inhibitor, dabigatran was found to be non-inferior to enoxaparin (except one study: REMOBILIZE). The details of these studies have been described in Table 4. Overall, lower rates of major, clinically relevant non-major (CRNM) and composite of major and CRNM bleeding were observed with apixaban; thus apixaban demonstrating superiority over LMWH in reducing VTE without a significant increase in the risk of bleeding.²⁷ The equivalence analysis of the three NOACs for thromboprophylaxis in orthopaedic surgery revealed that rivaroxaban and apixaban showed highest numerical effectiveness in the class of NOACs and were also proved to be equivalent in their effectiveness for thromboprophylaxis in orthopedic surgery.²⁸

The indirect comparison analysis of secondary prevention subgroups (previous stroke) between three NOACs by Bucher method was performed using data of three phase III trials (RE-LY, ROCKET-AF, and ARISTOTLE). The inter-trial differences in population characteristics were minimal in the secondary prevention cohort as apparent from comparable mean age, CHADS2 score, proportion of concurrent diabetes or hypertension and previous use of a vitamin K antagonist. Broadly, the results showed no substantial difference between three NOACs for efficacy and most safety endpoints. There were few striking differences within the NOACs; apixaban reported less number of myocardial infarction than dabigatran 150mg (hazard ratio 0.39, 95% CI 0.16 to 0.95) whereas hemorrhagic stroke (hazard ratio 0.15, 0.03 to 0.66), vascular death (0.64, 0.42 to 0.99), major bleeding (0.68, 0.47 to 0.99), and intracranial bleeding (0.27, 0.10 to 0.73) were less common with dabigatran 110 mg twice daily than with rivaroxaban.²⁹

Use of NOACs: Practical Issues and Considerations

Both European and American
### Table 4: VTE prophylaxis - clinical trial evidence

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Drug vs comparator</th>
<th>Indication</th>
<th>Efficacy Results: risk ratio</th>
<th>Safety Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eliquis trials</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Advance 1&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Apixaban 2.5 mg BID vs Enoxaparin 30 mg for 14d</td>
<td>TKR</td>
<td>1.02 (95% CI 0.78, 1.32)</td>
<td>0.7% vs. 1.4%, respectively; p=0.05</td>
</tr>
<tr>
<td>Advance 2&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Apixaban 2.5 mg BID vs Enoxaparin 40 mg QD for 14d</td>
<td>TKR</td>
<td>0.62 (95% CI 0.51, 0.74)</td>
<td>0.6% vs. 0.9%, respectively; p=0.30</td>
</tr>
<tr>
<td>Advance 3&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Apixaban 2.5 mg BID vs Enoxaparin 40 mg QD for 35d</td>
<td>THR</td>
<td>0.36 (95% CI 0.22, 0.54)</td>
<td>0.8% vs. 0.7%, respectively; p=0.54</td>
</tr>
<tr>
<td>Advance 1, 2 &amp; Phase II Study Pooled&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Apixaban regimens vs Enoxaparin regimens</td>
<td>TKR/THR</td>
<td>0.7% and 1.5%; risk diff: -0.8% (95% CI -1.2, -0.3)</td>
<td>4.4% and 4.9%; risk diff: -0.6% (95% CI -1.5 to 0.3)</td>
</tr>
<tr>
<td><strong>Xarelto Trials</strong></td>
<td></td>
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<tr>
<td>Record 1&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Rivaroxaban 10 mg QD 35 days vs Enoxaparin 40 mg QD 35 days</td>
<td>THR</td>
<td>0.30 (95% CI 0.18, 0.51)</td>
<td>0.3% vs. 0.1%, respectively; p=0.18</td>
</tr>
<tr>
<td>Record 2&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Rivaroxaban 10 mg QD 35 days vs Enoxaparin 40 mg QD 14 days</td>
<td>THR</td>
<td>0.21 (95% CI 0.13, 0.35)</td>
<td>&lt;0.1% vs. &lt;0.1%, respectively</td>
</tr>
<tr>
<td>Record 3&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Rivaroxaban 10 mg QD vs Enoxaparin 40 mg QD 14 days</td>
<td>THR</td>
<td>0.51 (95% CI 0.39, 0.65)</td>
<td>0.6% vs. 0.5%, respectively; p=0.77</td>
</tr>
<tr>
<td>Record 4&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Rivaroxaban 10 mg QD vs Enoxaparin 30 mg BID 14 days</td>
<td>THR</td>
<td>0.69 (95% CI 0.51, 0.92)</td>
<td>0.7% vs. 0.3%, respectively; p=0.11</td>
</tr>
<tr>
<td>Record 1-4&lt;sup&gt;56&lt;/sup&gt;</td>
<td>Rivaroxaban regimens vs Enoxaparin regimens</td>
<td>TKR/THR</td>
<td>0.42 (95% CI 0.29–0.63)</td>
<td>2.8% vs. 2.5%, respectively; p=0.19</td>
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<tr>
<td><strong>Pradaxa Trials</strong></td>
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<tr>
<td>Re-Novate&lt;sup&gt;57&lt;/sup&gt;</td>
<td>dabigatran 220 mg QD vs Dabigatran 150 mg QD vs Enoxaparin 40 mg QD for 35 days</td>
<td>THR</td>
<td>0.90 (95% CI 0.63, 1.29)</td>
<td>1.3% (150 mg) and 2.0% (220 mg) vs 1.6%, respectively; p=0.60 (150 mg), p=0.44 (220 mg)</td>
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<tr>
<td>Re-Novate II&lt;sup&gt;58&lt;/sup&gt;</td>
<td>dabigatran 220 mg QD vs Enoxaparin 40 mg QD for 35d</td>
<td>THR</td>
<td>0.88 (95 % CI 0.63, 1.22)</td>
<td>1.4% vs. 0.9%, respectively; p=0.40</td>
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<tr>
<td>Re-Model&lt;sup&gt;59&lt;/sup&gt;</td>
<td>dabigatran 220 mg QD vs Dabigatran 150 mg QD vs Enoxaparin 40 mg QD for 6-10d</td>
<td>THR</td>
<td>0.97 (95% CI 0.82, 1.13)</td>
<td>1.3% (150 mg) and 1.5% (220 mg) vs 1.3%, respectively; p=1.0 (150 mg), p=0.82 (220 mg)</td>
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<tr>
<td>Re-Mobilize&lt;sup&gt;60&lt;/sup&gt;</td>
<td>dabigatran 220 mg BID vs Dabigatran 150 mg BID vs Enoxaparin 30 mg BID for 12-15 days</td>
<td>THR</td>
<td>1.23 (95% CI 1.03, 1.47)</td>
<td>0.6% (150 mg) and 0.6% (220 mg) vs 1.4%, respectively</td>
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<tr>
<td>Dabigatran Pooled&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Dabigatran regimens vs Enoxaparin regimens</td>
<td>TKR/THR</td>
<td>1.03 (95% CI 0.93, 1.15)</td>
<td>1.1% (150 mg) and 1.4% (220 mg) vs 1.4%, respectively; p=0.54 (150 mg), p=0.19 (220 mg)</td>
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</table>

<sup>†Results obtained from article by Ageno 2012</sup>

Guidelines favor the use of NOACs though they also point out the limitations. Though NOACs are promising alternatives to warfarin, there are many practical aspects that require due consideration to ensure proper use of these drugs. Clinicians in India though eager to switch to NOAC, have approached these drugs with caution because of lack of knowledge on their proper use. Dr. Sachdeva, in his report states that shorter half-life of dabigatran may have implications in AF patients with poor compliance; with no INR guide and lack of antidotes for these drugs, reversal may be a big issue. Dose adjustment in hepatic and renal dysfunction and higher cost of these drugs compared to warfarin are of concern. There are unanswered questions around managing patients undergoing invasive or surgical procedures for prophylaxis of VTE. Currently, Indian physicians seek concrete information regarding crucial aspects of NOAC therapy such as measurement of anticoagulant effects, transition between different agents, ensuring drug intake compliance, dealing with dosing errors, management of bleeding complications etc. European Heart Rhythm Association (EHRA) has tried to address a few of these issues to provide a coordinated guidance to physicians.1

1. How to measure the anticoagulant effect of NOAC?

Unlike warfarin, NOACs do not require routine monitoring or dose adjustment except in emergency situations where the drug exposure assessment is required. Time delay between last intake and blood sampling should be recorded. The activated partial thromboplastin time (aPTT) shows a curvilinear response to dabigatran concentration and becomes incoagulable at higher concentrations. Trough aPTT level (12–24 h after ingestion) >2x ULN, indicates higher risk of bleeding. Similarly, prothrombin time (PT) provides information on presence of factor Xa inhibitors. Both aPTT and PT are qualitative indicators only and a normal aPTT or PT suggests that haemostatic function is not impaired because of the drug. Quantitative tests for DTI and FXa inhibitors...
2. Switching between anticoagulant regimens

Switching from VKAs to NOAC can be immediate if the INR is < 2.0. However, while switching from NOAC to warfarin, both should be administered concomitantly until the INR is in the desired range (about 5-10 days due to the slow onset of action of warfarin). Since NOACs may have an additional influence on INR during the overlap phase, INR should be measured just before the NOAC dosing and re-tested 24 hours after the last NOAC dose (i.e. sole warfarin therapy) to assure adequate anticoagulation. It is also recommended to closely monitor INR within the first month until stable values are attained (i.e. three consecutive measurements between 2 and 3).32

3. Ensuring compliance with NOAC intake

Ensuring compliance with NOAC intake is vital because the anticoagulant effect drops rapidly after 12–24 hours. Physicians should develop ways to optimize compliance which is known to be ≤80% for most drugs in daily practice. If low compliance persists, switch to VKAs may be appropriate.

4. How to deal with dosing errors?

In case of a missed dose, the forgotten dose can be taken up to six hours or up to 12 hours after the scheduled intake for a BID or QD regimen respectively. If this is not possible, the dose should be skipped and the next scheduled dose taken. Incase of a double dose on a BID regimen, next planned dose can be skipped and restarted BID after 24 hours while in OD dosing, normal regimen can be continued. In case of overdose, dialysis removes dabigatran though multiple sessions may be required due to its large distribution volume. Rivaroxaban and apixaban are not dialyzable.33

5. NOAC use in chronic kidney disease (CKD)

Approximately 80%, 33%, and 25% of dabigatran, rivaroxaban, and apixaban, respectively, are eliminated renally. Because data on NOAC safety and efficacy (even at reduced doses) is limited in patients with moderate to severe renal impairment, ACC/AHA/ESC guidelines recommend yearly monitoring of renal function (especially dabigatran). NOACs may be used in AF patients with mild or moderate CKD. Dose reductions are indicated in patients with CrCl ≤50 ml/min for apixaban and rivaroxaban.34 There are no outcome data for NOACs in patients with advanced chronic kidney disease (CrCl < 30 mL/min), and the current ESC guidelines recommend against their use in such patients although USFDA allows reduced doses of all three NOACs (CrCl: 15 to 29 mL/min: dabigatran: 75 mg BID, rivaroxaban 15 mg QD; apixaban: 2.5 mg BID). NOACs (except apixaban) should be avoided in AF patients with hemodialysis; VKAs may be preferable.35,33 Apixaban may be given in end stage renal disease patients maintained with hemodialysis; recommended dose is 5 mg BID (2.5 mg BID if age ≥80 years or body weight ≤60 kg)

6. Management of bleeding complications

Bleeding rates with NOACs are generally equal to or less than warfarin bleeding rates.36,37 There is no specific antidote for NOACs; in case of bleeding NOACs should be discontinued and assessment of hemodynamic stability, degree of anticoagulation and severity of bleeding should be done. Minor bleeding can be managed with simple delaying of the next dose. Moderate bleeding such as upper/lower GI can be managed by treating the bleeding source. Adequate diuresis, RBC transfusion, platelet substitution, fresh frozen plasma as plasma expander (not as reversal agent) and dialysis may be considered if required. For major life threatening bleeding, in addition to above measures, prothrombin complex concentrate (PCC) may be used.

7. When to stop and restart NOACs in patients undergoing surgical intervention

Common interventions with no clinically important bleeding risk can be performed at trough NOAC concentration (i.e. 12 or 24 hours after the last intake, depending on BID or QD regimen. Peri-operative NOAC interruption for dabigatran [1-2 days and 2-4 days depending upon CrCl in low and high bleeding risk respectively] is more than rivaroxaban/apixaban [1 and 2 days respectively for low and high bleeding risk]. Resumption of NOAC depends on hemostasis, bleeding risk and thromboembolic risk; NOACs could be recommenced as early as 12-24 hours (low bleeding risk and high thromboembolic risk) to >72 hours (high bleeding risk and low thromboembolic risk) post surgery upon ensuring hemostasis. Guidelines also recommend deferral of surgery by at least 12 hours, ideally 24 hours for emergency or trauma surgery when withdrawal of NOACs prior to surgery is inevitable.
Additionally, supportive care and withholding further doses is indicated. For AF patients undergoing PVI, a strategy of bridging with VKAs is preferred.

8. How to manage a patient with AF and Coronary Artery Disease (CAD)

There is a high prevalence of coronary artery disease (CAD) in AF patients ranging from 18-47%. NOAC is effective in AF while antiplatelet therapy is the standard management for CAD to reduce the risk of coronary events. In patients presenting with both AF and CAD, the choice of optimal long-term management to prevent both thromboembolic and CV events simultaneously is often challenging. Clinicians should assess stroke risk (CHA₂DS₂-VASc score), risk of coronary events [high risk (>3% annual death or MI), intermediate risk (1% to 3% annual death or MI), or low risk (<1% annual death or MI)], and bleeding risk (HAS-BLED) before making a treatment decision for such patients. As per 2014 ESC guideline recommendations, in patients with stable CAD and AF undergoing PCI at low bleeding risk (HAS-BLED 0–2), triple therapy (OAC, aspirin 75–100 mg daily, clopidogrel 75 mg daily) should be given for a minimum of 4 weeks (and no longer than 6 months) after PCI followed by dual therapy with OAC (NOAC or VKA) and clopidogrel (or aspirin) for up to 12 months; in those with high bleeding risk (HAS-BLED ≥3) dual therapy [OAC (NOAC or a VKA) + clopidogrel] for 4 weeks after PCI followed by dual therapy (OAC + clopidogrel or alternatively, aspirin) up to 12 months. Long-term antithrombotic therapy with OAC (i.e. whether NOAC or a VKA) (beyond 12 months) is recommended in all patients. The ACCP has concluded that the benefits of dual therapy (oral anticoagulation plus aspirin or clopidogrel) outweighs the risks for patients at high risk for stroke (eg, CHADS2 score ≥2) for the first 12 months after an acute coronary syndrome. However, for patients with a history of ischemic stroke or AF, and CAD, the usefulness of adding antiplatelet therapy to VKA therapy is uncertain for purposes of reducing the risk of ischemic cardiovascular events.

9. How to manage patients presenting with acute ICH or ischemic stroke while on NOAC?

Limited data is available regarding NOAC use in AF patients presenting with acute ICH or ischemic stroke. The coagulation status of patients under NOAC who have acute ICH should be corrected rapidly and NOAC should be discontinued. For ischemic stroke, thrombolytic therapy with recombinant tissue plasminogen activator is not recommended in patients taking NOACs because of increased bleeding risk within 48h of last NOAC dose. In case of uncertainty concerning last NOAC administration, prolonged aPTT (for dabigatran) or PT (for FXa inhibitors) indicates anticoagulation status. If NOACs have been administered within the last 48 hours and/or appropriate coagulation tests are not available or abnormal, alternative treatment option such as mechanical recanalization of occluded vessels maybe considered. Continuation of NOACs after ischemic stroke depends on the infarct size; as a rough guide the 1-3-6-12 day rule i.e., re-institution of anticoagulation in patients with transient ischemic attack after 1 day, with small infarct after 3 days, with a moderate stroke after 6 days, while large infarcts not before 2 (or even 3) weeks. NOACs may be restarted 10–14 days after ICH if cardio embolic risk is high and the risk of new intracerebral hemorrhage is estimated to be low. For patients with low cardio embolic risk and high bleeding risk, reinitiating of NOACs is contraindicated unless bleeding risk has been reversed. Non pharmacological strategies instead of NOACs (e.g. ablation or occlusion of the atrial appendage) may be considered in such subjects.

Conclusion

NOACs offer greater patient compliance, easier management, and improved thromboprophylaxis over traditional anticoagulants. Physicians across India are keen to use NOACs yet hesitant in view of some unanswered questions around them. Safety of NOACs in subjects with renal impairment, in those needing surgery or those presenting with bleeding complications or stroke while on NOACs need more clarity. Though ESC/EHRA offer very useful guidance to physicians across the globe pertaining to these issues, more consolidated opinions from physicians across India based on their experience with these drugs is much needed.

Acknowledgements

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