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COMMENTARY

Novel Oral Anticoagulants: A New Era in Anti-Thrombotic Therapy

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Abstract
For over half-a-century vitamin K antagonists (VKAs) served our patients well as effective anticoagulants, several novel oral anticoagulants (NOACs) have emerged and are now available as a suitable alternative for stroke prevention, venous thromboembolism prevention and treatment and to reduce vascular events in acute coronary syndrome. Compared to VKAs, the novel agents have several advantages including an improved efficacy/safety ratio, a faster onset of action, shorter plasma half-life, few drug or food interactions, and no requirement for regular monitoring. Although very promising in many regards their proper use will require new approaches in many daily aspects with dose adjustments may be required for patients with severe renal impairment or in the setting of drug interactions. The lack of specific antidote makes reversing their effect during bleeding or for emergency surgery particularly a major challenge. This article provides a focused overview on their current status.

Key Words: Anticoagulants, venous thromboembolism, novel oral anticoagulants, bleeding, atrial fibrillation

Introduction

In the current issue of *Ibnosina J Med BS*, Ali and Mustafa in their timely article "*Management of venous thromboembolism (VTE): from Leeches to NOACs*" highlighted the giant step which will revolutionize oral anticoagulation therapy through the introduction of the new oral anticoagulants (NOACs) to replace vitamin K antagonists (VKA) for the treatment of VTE (1). In addition to their enhanced convenience, NOACs are safer than warfarin because of the reduced risk of intracranial bleeding. They also have the potential to be more effective. This is particularly true in the community setting where the INR control with VKA is suboptimal. Their efficacy and safety are supported by extensive clinical studies (Table 1). Currently available NOACs; Dabigatran (*Pradaxa*), Rivaroxaban (*Xarelto*), and Apixaban (*Eliquis*), were all found to be at least as ef-

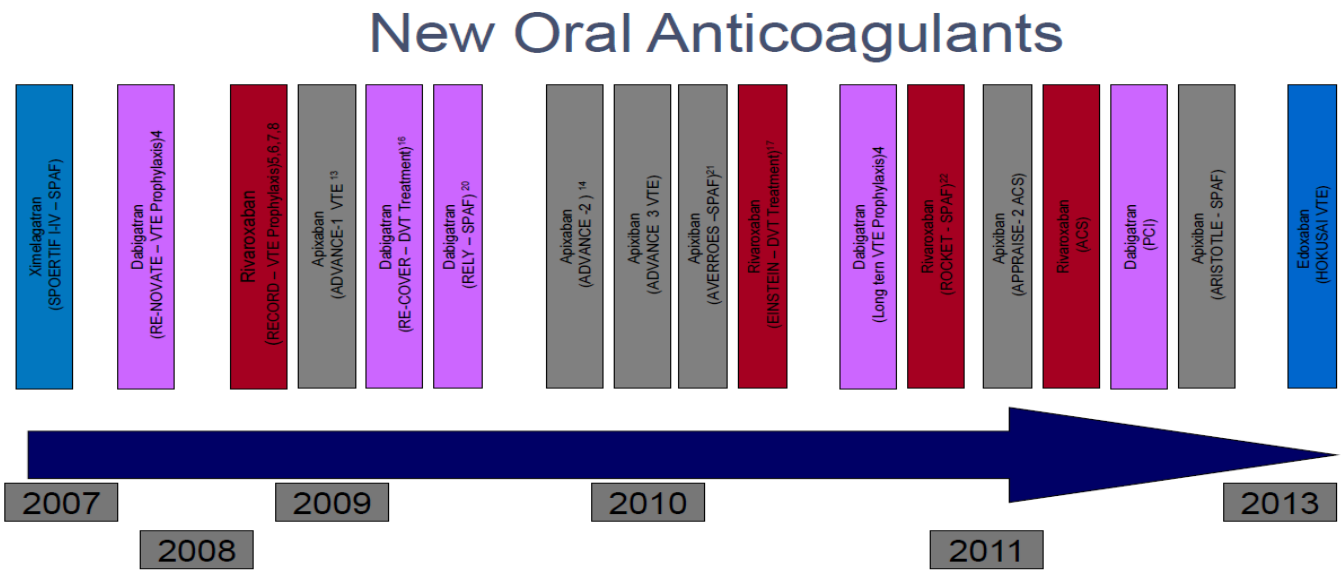

Table 1. NOACs clinical trials and development timeline

fective or superior to their compactors and are now licensed for several clinical indications (Table 2).

Key words: Anticoagulants, Oral.

Lessons from clinical trials

Most of the information comes from the large sized stroke prevention in atrial fibrillation (SPAF) studies (1-3) where NOACs have been compared with warfarin. Later data from studies for treatment of venous thromboembolism (4-20) were yielded to show similar and consistent non-inferiority compared to warfarin. Older patients who were at higher risk for both thromboembolic events and bleeding were enrolled. The clinical trials were illuminating and have taught us several lessons? Both class effects as well as differentiating features have emerged when NOACs are compared with VKAs.

Class effects

In patients with atrial fibrillation

The extensive clinical trials with the NOACs in patients with atrial fibrillation involving over 70,000 patients have shown several observations in common (1-3). All 3 NOACs (Dabigatran, Rivaroxaban and Apixaban) have been shown to be *robustly non-inferior to warfarin* for prevention of stroke (both ischaemic and haemorrhagic) or systemic embolism. All 3 NOACs were associated with *less intracranial bleeding* than warfarin. The rates of major bleeding were similar or lower than those with warfarin. The reduction in intracranial bleeding relative to warfarin is observed regardless of the time in therapeutic range (TTR) with warfarin. Thus, even in centers with the best international normalized ratio (INR) management, the risk of intracranial hemorrhage was lower with the NOACs than it was with warfarin. There was a proportionally similar, approximately 10% reduction in mortality with the NOACs compared with warfarin. There was no evidence of hepatic toxicity with any of the new agents, which was an important safety consideration after the experience with Ximelagatran. Therefore, in SPAF patients, we now have evidence that fixed-dose unmonitored anticoagulant therapy is at least as effective as well-controlled warfarin and is associated with less intracranial bleeding, the most feared complication of anticoagulant therapy.

In patients undergoing major orthopedic surgery

Extensive clinical trials have shown that NOACs are as effective as LMWH enoxaparin for thromboprophylaxis in patient undergoing major orthopedic surgery including total hip and total knee replacements (4-12). Furthermore, several studies have shown superiority of the NOACs compared to enoxaparin without an increase in bleeding events. There are no direct comparison of the different NOACs as

Table 2. Current Licensed Indications for use of the novel oral anti-coagulants
1. Prevention of venous thromboembolism in patients undergoing major orthopedic surgery.
2. Prevention of venous thromboembolism in medical inpatients (Rivaroxaban).
3. Prevention of stroke in patients with nonvalvular atrial fibrillation (SPAF).
4. Treatment of deep-vein thrombosis (DVT) and pulmonary embolism (PE) and to prevent recurrence of DVT and PE.
5. Prevention atherothrombotic events after an acute coronary syndrome (ACS) [Rivaroxaban (Xarelto) only so far].

Table 3. Guide for managing bleeding in these patients [consulting hematologist is recommended]

	Direct thrombin inhibitors (Dabigatran)	**FXa inhibitors (Apixaban, Rivaroxaban)**
Non-life-threatening bleeding	Ascertain timing for last dose+dosing regimen Estimate normalisation of "haemostasis" CrCl 50-80 ml/min:12-24 h CrCl 30-50 ml/min:24-36 h CrCl <30 ml/min:≥48 h Maintain diuresis Local haemostatic measures Fluid resuscitation Red cell transfusion if necessary Platelet transfusion in case of thrombocytopenia or platelet functional defect Consider dialysis (preliminary evidence-65% after 4 hrs.) Charcoal hemoperfusion (not recommended; no data)	Ascertain timing for last dose + dosing regimen Estimate normalisation of haemostasis: 12-24 hs Local haemostatic measures Fluid resuscitation Red cell transfusion if necessary Platelet transfusion in case of thrombocytopenia or platelet functional defect
Life threatening bleeding	All of the above Prothrombin concentrate complex (PCC) 25 IU/kg (may be repeated once or twice)-no evidence Activated PCC 50 IU/Kg, Max 200/kg/day: no strong data about additional benefits over PCC Activated r-VII (Novo seven), 90 IU/kg- only animal evidence	All of the above Prothrombin concentrate complex (PCC) 25 IU/kg (may be repeated once or twice)-no evidence Activated PCC 50 IU/Kg, Max 200/kg/day: no strong data about additional benefits over PCC Activated r-VII (Novo seven), 90 IU/kg- only animal evidence

yet but indirect comparison have suggested that Rivaroxaban performed better than Dabigatran for short prophylaxis (10 ± 5 days) and extended prophylaxis (34 ± 5 days) on the incidence of the composite VTE events. There was no difference between Apixaban and Rivaroxaban for this outcome for both treatment periods at 35 days. Finally, there were no differences in major bleeding events between all NOACs treatment regimens.

In patients with VTE

Similar results were obtained when Dabigatran or Rivaroxaban was compared with warfarin for treatment of patients with venous thromboembolism (13-20). Both agents were non-inferior to warfarin for prevention of recurrent venous thrombosis and were associated with less bleeding. With Dabigatran there was a significant reduction in any bleeding (the composite of major plus clinically relevant non-major bleeding), while Rivaroxaban was associated with significantly less major bleeding; at least in patients with pulmonary embolism.

Differences in study design

There were important differences in study design. Whilst, the trials with Dabigatran were double-blind and included patients with either deep vein thrombosis or pulmonary embolism, in both trials, patients were randomized to receive either Dabigatran or warfarin after initial treatment with a parenteral anticoagulant; heparin, low-molecular-weight heparin or Fondaparinux. By contrast, in the 2 open-label studies performed with Rivaroxaban; one in patients with deep vein thrombosis without overt evidence of pulmonary embolism and the other in patients with documented pulmonary embolism, patients in these trials were randomized to Rivaroxaban (given twice-daily doses for 3 weeks and once-daily thereafter), (without parenteral anticoagulant) or to conventional anticoagulation therapy, wherein patients were started on a parenteral anticoagulant and then transitioned to warfarin. The ongoing double-blind trial with Apixaban (twice daily throughout the trial, but a higher dose is used for the first week) includes patients with either deep vein thrombosis or pulmonary embolism and compares apixaban monotherapy (similar to Rivaroxaban studies) with conventional anticoagulation therapy.

In patients with acute coronary syndromes

Addition of a NOAC to antiplatelet therapy led to a modest reduction in cardiovascular events, which is most promising when added to single antiplatelet therapy associated with a substantial increase in bleeding, most pronounced in patients receiving dual antiplatelet therapy. Single antiplatelet treatment is rarely used because many ACS patients are treated with percutaneous coronary interventions and stents, for which guidelines recommend dual antiplatelet treatment. These conclusions have now been substantiated by data from seven double-blind, placebo-controlled phase II and III trials with over 30,000 patients enrolled. Using major adverse cardiovascular events (MACE) and clinically significant bleeding events as outcome measures, the following main results were yielded:

- Additional NOACs treatment in patients receiving single antiplatelet therapy decreased the rate of MACEs on average by 30% (21-23). The rate of bleeding events increased by 79%.
- Additional NOACs in patients treated with dual antiplatelet therapy, decreased the rate of MACEs by 13% but led to an increase in clinically significant bleeding rate by 134%.
- The gain in protection against MACEs was larger when adding an anticoagulant to single than to dual antiplatelet therapy (P = 0.03).
- Effects on bleeding were smaller when adding an anticoagulant to single than to dual antiplatelet therapy (P = 0.02).

Differentiating effects

There are several features that differentiate the NOACs from Warfarin:

- Slightly higher rate of myocardial infarction were observed with Dabigatran than with warfarin. It is unlikely that Dabigatran causes myocardial infarction because the rate of myocardial infarction was similar when Dabigatran was compared with placebo but it is more likely that Dabigatran is less effective than warfarin for prevention of myocardial infarction.
- More gastrointestinal bleeding with both Dabigatran (at least with the 150 mg twice-daily dose) and Rivaroxaban than with warfarin, particularly in the elderly. Although this phenomenon was not seen with Apixaban, it is interesting to note that in a comparison of rates of bleeding from various sites, the least difference between Apixaban and warfarin is in the rates of gastrointestinal bleeding.
- Compared with warfarin higher dose Dabigatran regimen (150 mg twice daily) reduced the rate of hemorrhagic stroke (number needed to treat to prevent one hemorrhagic stroke is 182), and reduced the rate of ischemic stroke with the number needed to treat with Dabigatran to prevent one ischemic stroke is 132.
- Compared with Warfarin, Apixaban the only NOAC associated with a reduction in stroke (both ischemic and hemorrhagic, but driven only by a reduction in hemorrhagic stroke) or systemic embolism *and also with less major bleeding* with numbers needed to treat to prevent one hemorrhagic stroke or one major bleed with Apixaban compared with warfarin are 238 and 67, respectively. Dabigatran, when administered at a dose of 110 mg twice daily, was also associated with significantly less intracranial bleeding and major bleeding than warfarin (numbers needed to treat to prevent one hemorrhagic stroke or one major bleed are 192 and 77 respectively).

NOACs Adverse reactions:

It is worthwhile illustrating the real life experience with NOACs outside clinical trial The report of French drug safety outlining their experience provides a "snap-shot" of all adverse reactions (ARs) reported to the "French Pharmacovigilance Network" since their launch until the end of

2012 (24-26):

1. **Dabigatran:** 1841 ARs were analyzed, hemorrhagic and thromboembolic ARs represent 36% (n=665) and 16% (n= 301) respectively. The most frequent bleeding sites were gastrointestinal tract (42%), hematuria (11%), intracranial (8%), epistaxis (8%). Thromboembolic ARs were mainly of venous origin (60%) The more serious thromboembolic effects were pulmonary embolism (3% n=57) and arterial thrombosis (4.7%, n=87, mainly ischemic stroke and myocardial infarction). Fifty eight patients died from bleeding (3%) and thirteen (0.7%) from thromboembolic events.

2. **Rivaroxaban:** 1033 ARs were reported, hemorrhagic and thromboembolic ARs associated with Rivaroxaban represented 41% (n=420) and 19% (n=201) respectively. These ARs were major in 37% of cases. The most frequent bleeding sites were surgical site (27%), gastrointestinal tract (21%), oral (15%), urinary (9%), and intracranial (9%). Thromboembolic ARs were mainly of venous origin (86%). The more serious effects were pulmonary embolism (5.7%, 59 cases) and ischemic stroke (1%, 14 cases). Seventeen patients (1.7%) died from bleeding, and ten (1%) from thromboembolic event.

NOACs and gastrointestinal bleeding:
This association is very important and worth exploring in more details. NOACs were associated with a modestly increased risk of gastrointestinal (GI) bleeding (27-31). This risk is highest in patients treated for thrombosis (ACS and DVT/PE). The higher risk in ACS is possibly due to the fact that NOACs were administered on top of other antithrombotic medication, thereby cumulating risks. In a large meta-analysis on the risk of GI bleeding and also risk of clinically relevant bleeding attributable to use of NOAC, a total of 43 trials were included, comprising data on more than 125,000 patients. Only 44% of trials reported GI bleeding separately. Over 1100 events were reported in over 75000 patients (1.5% from 17 trials). These were predominantly major bleeds (89%). The percentage of GI bleeds per trial was low for the NOAC group in trials on orthopaedic surgery (0.1% for NOAC, 0.2% for controls), intermediate in trials on atrial fibrillation (NOACs: 2.1%, control: 1.6%) and deep venous thrombosis/pulmonary embolism (DVT/PE) (NOAC: 3.0% vs. 1.9% in control), and high in trials on acute coronary syndrome (ACS) (NOACs: 5.3%, control: 1.0%). Four out of 17 studies showed an increased risk of GI bleeding with NOACs, 12 a comparable risk and 1 a lower risk. No difference was seen in GI bleeding risk between therapeutic or prophylactic use of NOACs. When all 43 trials included on clinically relevant bleeding, the overall risk was significantly higher with the use of NOACs (OR: 1.16, 95%CI: 1.00-1.34). Patients treated for ACS had an increased risk of bleeding (OR: 2.06), while other indications did not show a statistically significant increased risk.

Possible measures to take in case of bleeding:
Risk of bleeding remains the most concerning adverse effect with NOACs in particular in the absence of a specific antidoate (32-33). Treatment of bleeding remains supportive and requires special knowledge of these agents including mechanism of action, laboratory evaluation and resuscitation skills. A guide for managing bleeding in these patients is given in Table 2. Consulting haematologist is strongly recommended.

Cost effectiveness
In a Markov decision-analysis model, data from clinical trials were incorporated to evaluate lifetime costs and quality-adjusted life-years of NOACs compared with warfarin (34). The willingness-to-pay threshold was USD 50,000/ quality-adjusted life-years (QUALY) gained. Warfarin had the lowest cost of USD 77,813 followed by Rivaroxaban 20 mg (USD 78,738). Dabigatran 150 mg (USD 82,719), and Apixaban 5 mg (USD 85,326). Apixaban 5 mg had the highest QUALY estimate at 8.47, followed by Dabigatran 150 mg (mean 8.41), Rivaroxaban 20 mg (mean 8.26), and warfarin (mean 7.97). In a Monte Carlo probabilistic sensitivity analysis, Apixaban 5 mg, Dabigatran 150 mg, Rivaroxaban 20 mg, and warfarin were cost-effective in 45.1%, 40%, 14.9%, and 0% of the simulations, respectively. In patients with nonvalvular atrial fibrillation and an increased risk of stroke prophylaxis, Apixaban 5 mg, Dabigatran 150 mg, and Rivaroxaban 20 mg were all cost-effective alternatives to warfarin. The cost-effectiveness of novel oral anticoagulants was dependent on therapy pricing in the United States.

In a study (34) aimed to evaluate the medical cost reductions associated with the use of individual NOACs instead of warfarin from the US payer perspective based on NOACs are effective options for SPAF patients as concluded by RE-LY, ROCKET-AF, and ARISTOTLE. In a patient year, the medical cost reduction associated with usage of NOAC instead of warfarin was estimated to be 179, 89, and 485 for Dabigatran, Rivaroxaban, and Apixaban, respectively. When clinical event rates and costs were allowed to vary simultaneously, through a Monte Carlo simulation, the 95% confidence interval of annual medical costs differenc-

es ranged between -USD 424 and +USD 71 for Dabigatran, -USD 301 and +USD 135 for Rivaroxaban, and –USD 741 and –USD 252 for Apixaban, with a negative number indicating a cost reduction. The study concluded that, usage of the NOACs, Dabigatran, Rivaroxaban, and Apixaban may be associated with lower medical (excluding drug costs) costs relative to warfarin, with Apixaban having the most substantial medical cost reduction. These data are based on efficacy outcomes form clinical trials rather than real life experience with NOACs, therefore more data will be needed to affirm the cost effectiveness.

Concluding remarks and way forward

The NOACs represent major landmark advancement in anticoagulant care since they overcome many of the limitations of traditional antithrombotic therapies. NOACs are efficacious alternative antithrombotic to VKAs and associated with favourable and predictable PK and PD, less drug and food interactions and therefore, no need for monitoring. More NOAC agents in the pipeline including Darexaban, Betrixabanare, these will strengthen our armamentarium for stroke and VTE prevention and for VTE and ACS therapy. Their safety is enhanced by the reduced risk of intracranial bleeding. There is associated increased risk of GI bleeding in patients treated for ACS and VTE. The search for specific antidotes is in Ernst. This will hopefully enhance their safety and increase their application. From health economics perspective, whilst NOACs for the initial management of VTE (first 3 months) are cheaper than current therapy, their long term cost-effectiveness remains questionable. For SPAF, NOACs were found to be cost-effective based on clinical trial outcome data rather than on real life analysis. After over 50 years of domination of VKA as effective anithrombotics, NOACs are now here and making a huge impression, and will stay for long time.

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