Non-vitamin K antagonist oral anticoagulants (NOAC)

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ABSTRACT

Options for anticoagulation have been expanding steadily over the past few decades, providing a greater number of agents for prevention and management of thromboembolic disease. In addition to heparins and vitamin K antagonists, anticoagulants that directly target the enzymatic activity of thrombin and factor Xa have been developed. Appropriate use of these agents requires knowledge of their individual characteristics, risks, and benefits. This article review article discusses practical aspects of the use of Non-vitamin K antagonist the New Oral AntiCoagulants (NOACs).

Introduction :

Non-vitamin K antagonist oral anticoagulants (NOACs) or Initially referred to as Novel oral anticoagulants or now called Direct oral anticoagulants (DOACs) are an alternative for vitamin K antagonists (VKAs) to prevent stroke in patients with atrial fibrillation (AF).[1-3] Ultimately, both terms are interchangeable when referring to the direct factor Xa inhibitors - apixaban, edoxaban, and rivaroxaban as well as the direct thrombin inhibitor dabigatran. Non-vitamin K antagonist oral anticoagulants have an improved efficacy / safety ratio, a predictable anticoagulant effect without need for routine coagulation monitoring, and fewer food and drug interactions compared with VKAs.

Mechanisms of Action:

Dabigatran an oral direct thrombin inhibitor (DTI), was the first NOAC to be approved for stroke prevention in atrial fibrillation; rivaroxaban and apixaban, direct factor Xa (FXa) inhibitors followed dabigatran.

Hemostasis involves several processes. These include platelet activation, generation of fibrin by activated coagulation factors, inhibition of procoagulant factors to prevent excessive clot propagation, and fibrinolysis to dissolve the fibrin clot as the endothelial surface is repaired ***(Figure 1 and Figure 2).*** Although these processes are often described separately, there are multiple points of overlap between platelets, procoagulant factors, endogenous anticoagulant and fibrinolytic factors, and the endothelium, to promote an appropriate level of hemostasis and limit clot formation to sites of vessel injury. The direct thrombin inhibitors and direct factor Xa inhibitors block major procoagulant activities involved in the generation of a fibrin clot ***(Figure 3).***

Thrombin is the final effector in blood coagulation and factor X positioned at the convergence of the extrinsic and intrinsic pathways of coagulation constitute good targets for anticoagulation. Additionally, dabigatran by inhibiting fibrin-bound thrombin and rivaroxaban, apixaban by inhibiting FXa assembled within the prothrombinase complex have efficacy advantages over indirect thrombin inhibitors (heparin or LMWH) and indirect FXa inhibitors (fondaparinux) respectively.[6]

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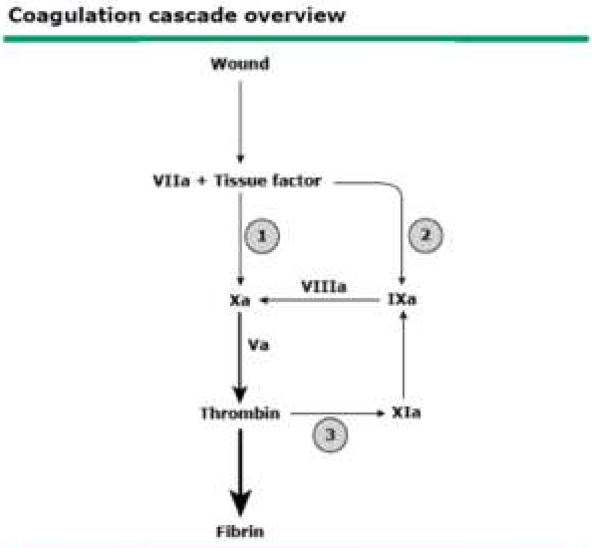
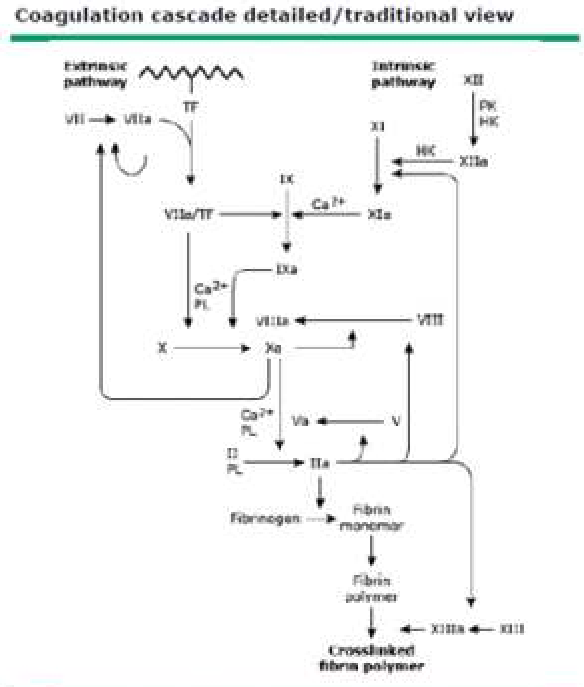


This schematic shows a revised version of the coagulation cascade that emphasizes the importance of pathways for hemostasis in vivo. Tissue factor exposed at a wound interacts with factor VIIa and initiates clotting by two pathways: (1) activation of factor X to Xa (ie, the extrinsic ten-ase complex) and (2) conversion of factor IX to IXa, which activates factor X to Xa (ie, the intrinsic ten-ase complex). Pathways 1 and 2 are equally important.
In a third pathway (3), thrombin also activates factor XI to XIa, which can lead to further generation of factor IXa; it serves as an amplification pathway required during severe hemostatic challenges.
Coagulation factors are shown as Roman numerals. Only the activated forms (with the suffix "a") are shown in this diagram for simplicity. Thrombin is factor IIa.

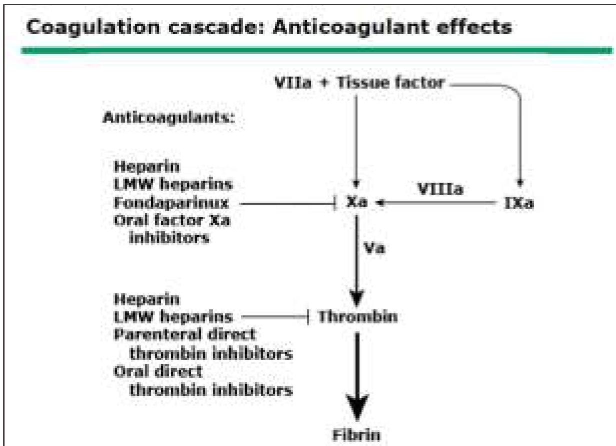


Schematic representation of the coagulation cascade including our improved understanding of the role of the tissue factor (TF) pathway in initiating clotting, interactions between pathways, and the role of thrombin in sustaining the cascade by feedback activation of coagulation factors.

PK: prekallikrein; HK: high molecular weight kininogen; PL: phospholipid.

Adapted from: Ferguson JD, Banning AP. Spontaneous intramural aortic haematoma: incidence, prognosis and complications. Eur Heart J 1990; Suppl 19:8.

Figure 1 and 2 : **Source : 2019 Up To Date**



LMW heparins include enoxaparin, dalteparin, and tinzaparin. Unfractionated heparin and LMW heparin inhibit both factor Xa and thrombin; the effect of LMW heparins on thrombin is less than that of unfractionated heparin. Fondaparinux is a synthetic pentasaccharide based on the minimal antithrombin-binding region of heparin that inhibits factor Xa. LMW heparins, unfractionated heparin, and fondaparinux inhibit clotting factors by binding to antithrombin.
Oral direct factor Xa inhibitors include apixaban, rivaroxaban, and edoxaban. Parenteral direct thrombin inhibitors include argatroban and lepirudin. Oral direct thrombin inhibitors include dabigatran.
Coagulation factors are shown as Roman numerals. Only the activated forms (with the suffix "a") are shown for simplicity. Thrombin is also known as factor IIa.

LMW: low molecular weight.

Figure 3

Pharmacology :

NOACs have pharmacologic advantages over warfarin such as predictable pharmacokinetics, drug interactions, wide therapeutic window and these properties along with their dosage regimen in approved indications are summarized in table below.[7,8,9]

		Dabigatran	Rivaroxaban	Apixaban
Pharmacology	Mechanism of action	Selective direct thrombin inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor
	Oral bioavailability %	6	80–100	50
	Protein Binding %	35	95	87
	T max	0.5–2 h	1 to 4 h	1 to 4 h
	Half-life	12 to 17 h	5 to 13 h	8 to 15 h
	Renal elimination	85%	66 (36 unchanged and 30 inactive metabolites)	25%
	Food effect	Delays absorption	Delays absorption	Not reported
	Effect of age	None	Variable	Not reported
	Effect of body weight	None	None	Not reported
Drug interactions	CYP3A4	None	Yes; potent inhibitors of CYP3A4 and P-gp*: avoid; Potent inducers of CYP3A4‡ and P-gp: use with caution	Yes; potent inhibitors of CYP3A4 and P-gp*: avoid; Potent inducers of CYP3A4‡ and P-gp† use with caution
	P-glycoprotein	Yes; verapamil, reduce dose; dronedarone: avoid; Potent inducers of P-gp†: avoid		
	Means to monitor interaction	No	No	No
Approved indications and dosage regimens	Atrial fibrillation	Creatinine clearance (CrCl): ≥ 30 mL/min: 150 mg BID 15-29 mL/min: 75 mg BID	CrCl: > 50 mL/min: 20 mg QD 15-50 mL/min: 15 mg QD	5 mg BID; 2.5 mg BID if any 2 of the following 3 are present: 1. age ≥ 80 y 2. weight ≤ 60 kg, or 3. serum creatinine ≥1.5mg/dl
	Venous thrombosis	CrCl >30 mL/min: 150 mg orally, twice daily after 5-10 days of parenteral anticoagulation	Initial treatment: 15 mg BID for 3 wk, then 20 mg QD for remaining treatment period; prevention of recurrent VTE: 20 mg QD daily; contraindicated if creatinine clearance< 30 mL/min	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*

**Potent inhibitors of CYP3A4 include antifungals (e.g., ketoconazole, intraconazole, voriconazole, posaconazole), chloramphenicol, clarithromycin, and protease inhibitors (e.g., ritonavir, atanazavir). 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.*

Source : Jamshed J Dalal, Anil Dhall, Abhay Bhave. Current Perspective on Use of NOAC in Clinical Practice in India. Journal of The Association of Physicians of India ■ Vol. 64 ■ April 2016

Indications and Contraindiactions :

Non-vitamin K antagonist oral anticoagulants are approved for stroke prevention in non-valvular atrial fibrillation. Strictly the term non valvular AF refers to AF in the absence of a mechanical prosthetic heart valve or moderate to severe mitral stenosis (usually of rheumatic origin) ***(Table 1)*** [3,4,5]. Essentially all other native valvular stenoses and insufficiencies as well as mitral valve repair, bioprosthetic valve replacements (exception may be AF in the presence of a biological mitral prosthesis implanted for rheumatic mitral stenosis) and transaortic valve intervention (TAVI) may be treated with NOACs.[5]

Table 1 Selected indications and contraindications for non-vitamin K antagonist oral anticoagulant therapy in atrial fibrillation patients

Condition	Eligibility for NOAC therapy
Mechanical prosthetic valve	Contraindicated
Moderate to severe mitral stenosis (usually of rheumatic origin)	Contraindicated
Mild to moderate other native valvular disease (e.g., mild-moderate aortic stenosis or regurgitation, degenerative mitral regurgitation etc.)	Included in NOAC trials
Severe aortic stenosis	Limited data (excluded in RE-LY) Most will undergo intervention
Bioprosthetic valve (after > 3 months post operatively)	Not advised if for rheumatic mitral stenosis Acceptable if for degenerative mitral regurgitation or in the aortic position
Mitral valve repair (after > 3 months post operatively)	Some patients included in some NOAC trials
PTAV and TAVI	No prospective data yet May require combination with single or dual antiplatelet therapy
Hypertrophic cardiomyopathy	Few data, but patients may be eligible for NOACs

Hatched—limited data.
PTAV, percutaneous transluminal aortic valvuloplasty; TAVI, transcatheter aortic valve implantation.

Source : Jan Steffel, Peter Verhamme, Tatjana S. Potpara et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin Kantagonist oral anticoagulants in patients with atrial fibrillation. European Heart Journal (2018) 39, 1330-1393

Recommended Doses of NOAC in AF for Stroke Prevention :

Stroke prevention in atrial fibrillation (SPAF)		
	Standard dose	Comments/dose reduction
Apixaban[30]	2 × 5 mg	2 × 2.5 mg if two out of three: weight ≤60 kg, age ≥80 years, serum creatinine ≥133 μmol/(1.5 mg/dL) [or if CrCl 15–29 mL/min]
Dabigatran[28]	2 × 150 mg / 2 × 110 mg	No pre-specified dose-reduction criteria[a]
Edoxaban[31]	1 × 60 mg	1 × 30 mg if: weight ≤60 kg, CrCl ≤50 mL/min, concomitant therapy with strong P-Gp inhibitor (see **chapter 5**)
Rivaroxaban[29]	1 × 20 mg	1 × 15 mg if CrCl ≤50 mL/min

Risk Stratification:

Approximately 15% of strokes are associated with AF and the incidence increases with age.[10] 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. 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).[11] CHA2DS2-VASc, an adaptation of

CHADS2 incorporates additional risk factors: vascular disease, age 65-74 years, and female gender. The European Society of Cardiology (ESC) guidelines recommend OACs for patients with a CHADS2 score $\geq$ 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).[12] Direct comparison of VKA and aspirin in nine studies demonstrated VKAs to be superior to aspirin with a relative risk (RR) reduction of 39%.

Clinical Trials :

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 5 mg bid), or at least non-inferior with a similar rate of hemorrhage (rivaroxaban 20 mg) or a lower rate of

CHADS Score

Comparison of the CHADS2 and CHA2DS2-VASc risk stratification scores for subjects with nonvalvular AF

Definition and scores for $CHADS_2$ and CHA_2DS_2-VASc

$CHADS_2$ acronym	Score
Congestive HF	1
Hypertension	1
Age ≥75 years	1
Diabetes mellitus	1
Stroke/TIA/TE	2
Maximum score	6
CHA_2DS_2-VASc acronym	**Score**
Congestive HF	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Age 65 to 74 years	1
Sex category (ie, female sex)	1
Maximum score	9

Stroke risk stratification with the $CHADS_2$ and CHA_2DS_2-VASc scores

$CHADS_2$ acronym	Unadjusted ischemic stroke rate (% per year)*
0	0.6%
1	3.0%
2	4.2%
3	7.1%
4	11.1%
5	12.5%
6	13.0%
CHA_2DS_2-VASc acronym	**Unadjusted ischemic stroke rate (% per year)***
0	0.2%
1	0.6%
2	2.2%
3	3.2%
4	4.8%
5	7.2%
6	9.7%
7	11.2%
8	10.8%
9	12.2%

AF: atrial fibrillation; $CHADS_2$: Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Prior Stroke or TIA or Thromboembolism (doubled); CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, Prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65-74 years, Sex category; HF: heart failure; LV: left ventricular; MI: myocardial infarction; PAD: peripheral artery disease; TE: thromboembolic; TIA: transient ischemic attack.

* These unadjusted (not adjusted for possible use of aspirin) stroke rates were published in 2012[1]. Actual rates of stroke in contemporary cohorts might vary from these estimates.

Reference:

1. *Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J 2012;*

hemorrhage (dabigatran 110 mg bid, apixaban 5 mg bid). The results of these trials are described in detail in the table below.[13,14,15] 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. 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.

Results from pivotal phase III trials[13,14,15]

Trial Name	Interventions	Patient baseline/ characteristics	Efficacy results	Safety outcome
RE-LY: Randomized, open-label, parallel-group, multicentre non-inferiority trial	Dabigatran etexilate 110 mg bid (blinded) or Dabigatran etexilate 150 mg bid (blinded) Vs Open-label warfarin (INR 2-3). n =18,113)	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	Composite of stroke and SE: D110 mg vs. Warf: RR 0.91 (95% CI: 0.74–1.11); P value (non-inferiority) <0.001 D150 mg vs. Warf: RR 0.66 (95% CI: 0.53-0.82); P value (superiority)< 0.001; RR 0.65 (95% CI: 0.52–0.81); P value (superiority)< 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	Major bleeding*: D110 mg vs. warf: RR 0.80 (95% CI: 0.70–0.93); P (superiority) = 0.003; D150 mg vs. Warf: RR 0.93 (95% CI: 0.81–1.07); P (superiority) = 0.32 Intracranial bleeding: D110 mg vs. Warf: RR: 0 0.31 (0.20–0.47) p-value = <0.001; D150 mg vs. Warf- RR: 0.40 (0.27–0.60) p-value <0.001 GI bleeding: D110 mg vs. Warf: RR: 1.10 (0.86–1.41) p-value 0.43; D 150 mg vs. Warf- RR: 1.50 (1.19–1.89) p-value <0.001
Rocket-AF: Randomized, double-blind, double-dummy, parallel-group, multicentre non-inferiority trial	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)	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	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<0.001 MI events 0.9% and 1.1% per year in rivaroxaban and warf 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	Major and non-major clinically relevant bleeding^: 14.9% & 14.5% per year in rivaroxaban and warf respectively; HR, 1.03; 95% CI, 0.96 to 1.11; P = 0.44) Intracranial bleeding: 0.5% vs. 0.7%, P = 0.02 and fatal bleeding 0.2% vs. 0.5%, P = 0.003 in rivaroxaban and warf respectively GI bleeding: 3.2% and 2.2% in rivaroxaban and warf respectively, P<0.001
Aristotle- Randomized, double blind, double- dummy, active (warfarin) controlled non-inferiority trial	Apixaban (5 mg bid or 2.5 mg bid for pts with ≥2 of the following at baseline: age ≥80 yrs, body weight ≤60 kg, serum creatinine ≥1.5 mg/dL) Vs Double-blind warfarin (INR 2-3). n = 18 201	Age: 70 (median) $CHADS_2$: 2.1 ± 1.1 (mean ± SD) Similar distribution of co-morbidities: Prior stroke/transient ischemic attack: 3538 Hypertension: 15916 Diabetes: 4547	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<0.001 for noninferiority; P=0.01 for superiority MI events: 0.53 vs 0.61 in apixaban and warf respectively HR: 0.88 (0.66-1.17) p- value: 0.37 All-cause mortality: 3.52% vs 3.94% in apixaban and warf respectively HR: 0.89; 95% CI (0.80 to 0.998; P = 0.047).	Major bleeding* Apixaban (2.13%) vs. warf (3.09%): HR 0.69 (95% CI: 0.60-0.80); P< 0.001 Intracranial bleeding: 0.33 vs 0.80 per year in apixaban and warf respectively, HR: 0.42 (0.30-0.58); p-value <0.001 GI bleeding: 0.76 vs 0.86 per year in apixaban and warf respectively; HR 0.89 (0.70-1.15) p-value= 0.37

*Hb drop ≥2 g/dL, transfusion ≥2 units of blood, bleeding in critical area or organ, life-threatening bleeding; ^clinically overt bleeding associated with fatal outcome, involving a critical site, Hb drop ≥2 g/dL, transfusion ≥2 units of packed RBCs or whole blood; *clinically overt bleeding plus ≥1 of: Hb drop ≥2 g/dL; transfusion of ≥2 units of packed RBCs; fatal bleeding or bleeding that occurs in ≥1 critical site

Source : Jamshed J Dalal, Anil Dhall, Abhay Bhave. Current Perspective on Use of NOAC in Clinical Practice in India. Journal of The Association of Physicians of India ■ Vol. 64 ■ April 2016

Switching Between Anticoagulant Regimens

When switching between different anticoagulant therapies, it is important to ensure the continuation of anticoagulant therapy while minimizing the risk for bleeding.

Vitamin K antagonist to non-vitamin K antagonist oral anticoagulant : The NOAC can immediately be initiated once the INR is < 2.0. If the INR is 2.0-2.5, NOACs can be started immediately or (better) the next day. For INR > 2.5, NOAC can be started when INR is <_3 for rivaroxaban, <_2.5 for edoxaban, and <_2 for apixaban and dabigatran.[16]

Non-vitamin K antagonist oral anticoagulant (NOAC) and Vitamin K antagonist (VKA) : The NOAC and VKA should be administered concomitantly until the INR is in a range that is considered appropriate, similar to the situation when low molecular weight heparins (LMWHs) are administered during VKA initiation.[16]

Non-vitamin K antagonist oral anticoagulant to parenteral anticoagulants : The parenteral anticoagulant [unfractionated heparin (UFH) and LMWH] can be initiated when the next dose of the NOAC would be due.[16]

Parenteral anticoagulant to non-vitamin K antagonist oral anticoagulant :

Intravenous UFH : NOACs can usually be started 2 h after intravenous UFH (half-life 2 h) is discontinued.

Low molecular weight heparin : NOACs can be initiated when the next dose of LMWH would be due.[16]

Non-vitamin K antagonist oral anticoagulant to non-vitamin K antagonist oral anticoagulant : The alternative NOAC can be initiated when the next dose of the initial NOAC is due, except in situations where higher than therapeutic plasma concentrations are expected (e.g. in a patient with impaired renal function). In such situations, a longer interval in between NOACs is recommended.[16]

Aspirin or clopidogrel to non-vitamin K antagonist oral anticoagulant : The NOAC can be started immediately and aspirin or clopidogrelstopped, unless combination therapy is deemed necessary.[16]

Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Kidney Disease

Dabigatran has the greatest extent of renal elimination (80%), whereas 50%, 35%, and 27% of edoxaban, rivaroxaban, and apixaban, respectively. In situations with acute renal failure, any NOAC therapy needs to be discontinued and parenteral anticoagulation initiated. 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. There are no outcome data for NOACs in patients with advanced chronic kidney disease (CrCL < 30 mL/min) The efficacy and safety of NOACs in patients with end-stage renal dysfunction and on dialysis is unclear and subject to ongoing studies. There are no data on the use of NOACs in AF patients after kidney transplantation.

Non-Vitamin K Antagonist Oral Anticoagulants in Liver Disease

All four NOACs are contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including Child-Turcotte-Pugh C cirrhosis. Rivaroxaban should also not be used in AF patients with Child B liver cirrhosis due to a > two fold increase in drug exposure in these patients. Dabigatran, apixaban and edoxaban may be used with caution in patients with Child B cirrhosis.[16]

Measurement of Anticoagulant Effect of NOAC

Unlike warfarin, NOACs do not require routine monitoring. 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. [thrombin clotting time (TT), activated clotting time

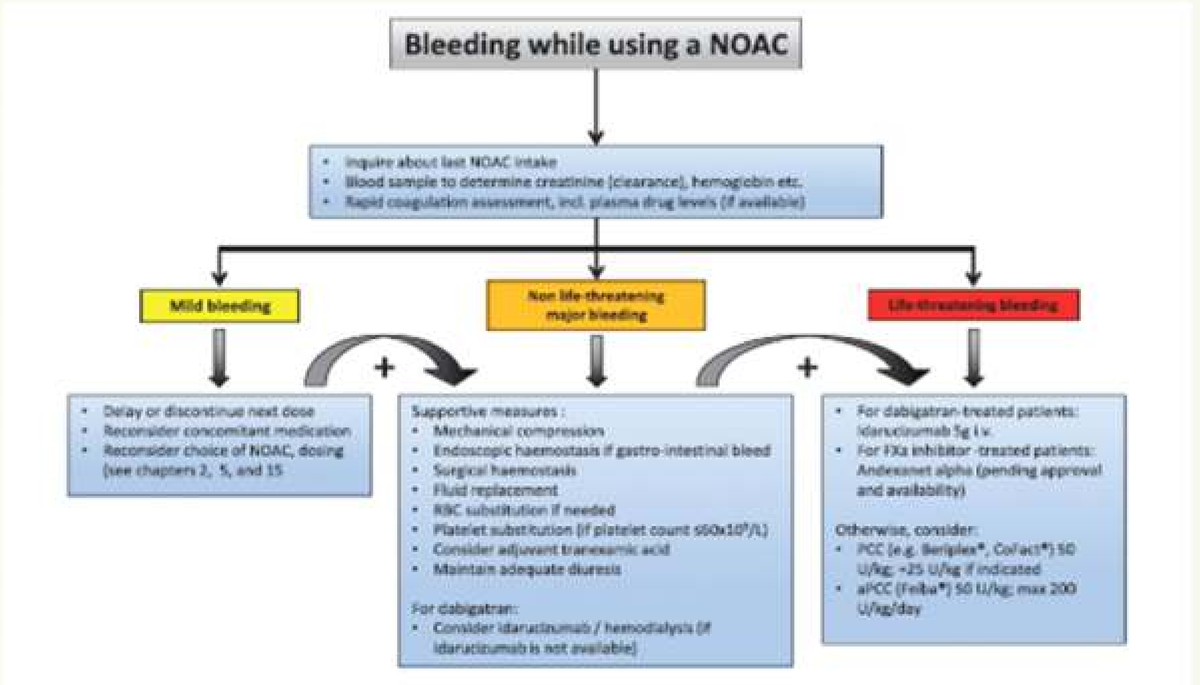
(ACT)] are sensitive tests to evaluate the anticoagulant effects of dabigatran but are not routinely available in hospitals.[17,18]

Management of Bleeding on NOAC:

Bleeding rates with NOACs are generally equal to or less than warfarin bleeding rates. 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.

Surgical Intervention in Patients on NOAC :

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. If an emergency intervention is required, the NOAC should be discontinued immediately. Specific management will then depend on the level or urgency.



Source : Jan Steffel, Peter Verhamme, Tatjana S. Potpara et al.The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin Kantagonist oral anticoagulants in patients with atrial fibrillation.European Heart Journal (2018) 39, 13301393

Patient with Atrial Fibrillation and Coronary Artery Disease

In patients presenting with both AF and CAD, the choice of optimal long-term management to prevent both thrombo embolic 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 (HASBLED) 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 02), 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 upto 12 months; in those with high bleeding risk (HAS-BLED > 3) dual therapy [OAC (NOAC or aVKA) + clopidogrel] for 4 weeks after PCI followed by dual therapy (OAC clopidogrelor alternatively, aspirin) upto 12 months. Long-term antithrombotic therapy with OAC (i.e. whether NOAC ora VKA) (beyond 12 months) is recommended in all patients. The ACCP has concluded that the benefits of dual therapy (oral anticoagulation plus aspirin orclopidogrel) 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.

Intracranial Hemorrhage or Ischemic Stroke While on NOAC

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 48 h 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., Reinstitution of anticoagulation in patients with transient ischemic attack after 1 day, with small infarct after 3 days, with a moderate stroke after 6days, 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.

Women of Reproductive Age

All OAC use should be considered with caution in women of child bearing age and an appropriate test to rule out pregnancy and contraceptive counselling advice arranged before initiation of any agent. Importantly, NOACs are contraindicated in pregnancy as well as during breast feeding.

Conclusion :

The direct thrombin inhibitors and direct factor Xa inhibitors act at major points in the coagulation cascade that appear to be rate-limiting in clotformation. These drugs inactivate both circulating and clotbound activated coagulation factors, and they do not induce antiplatelet antibodies, features that may have advantages in specific clinical settings. A major advantage of these agents is the lack of a requirement for monitoring, due to less variability in drug effect for a given dose. NOACs offer greater patient compliance, easier management, and improved thromboprophyl axisover traditional anticoagulants. However, the DOACs are expensive, their half-lives are short, they are not appropriate for all indications, and compliance is more difficult to monitor than vitamin K antagonists. Their use is not appropriate inpatients with severe renal insufficiency, severe liver disease pregnancy, antiphospholipid syndrome (APS), or prosthetic heart valves. Laboratory testing prior to administration of these agents should includeprothrombin time (PT) and activated partial thromboplastin time (aPTT), to assess and document coagulation status before anticoagulation; and measurement of serum creatinine, as a baseline and for potential dose adjustment in the event of renal insufficiency. Patients with impaired renal function should have appropriate dose reduction or drug avoidance depending on the creatinine clearance. The goal when transitioning between anticoagulants is to maintain stable anticoagulation. When transitioning between a DOAC and a vitamin Kantagonist, it is important to keep in mind that the full effect of the VKA does not occur for the first few days. When transitioning from a VKA to a DOAC, it is important to keep in mind that the resolution of VKA effect may take several days.

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