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Review Article

Direct acting oral anticoagulant: Bench to bedside

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ABSTRACT

Vitamin K antagonists are an effective group of oral anticoagulants. However because of genetic variability in their metabolism and multiple food and drug interactions, these drugs have narrow therapeutic window with unpredictable anticoagulant effects requiring constant monitoring. Several newer direct acting oral anticoagulants have been approved for prevention of stroke in patients with nonvalvular atrial fibrillation and treatment or prevention of venous thromboembolism. The direct acting oral anticoagulants include the direct thrombin inhibitor (dabigatran) and the factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban). These have a better safety and efficacy profile compared to Vitamin K antagonists. Some of the limitations of these drugs include increased risk of gastrointestinal bleeding (except apixaban), increased risk for thrombotic complication upon sudden cessation of therapy and inability to monitor the anticoagulation efficacy. Recent availability of the antidote to these drugs has further strengthened their safety profile. In the current review we will discuss these agents with focus on their potential clinical uses and limitations.

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Introduction

Vitamin K antagonists (VKA) have till recently been the only oral anticoagulants for stroke prevention in patients with nonvalvular atrial fibrillation (AF) and treatment or prevention of venous thromboembolism (VTE). They have reduced the incidence of stroke by two-thirds in patients with nonvalvular AF.¹ Anticoagulation potential of VKA is often suboptimal due to genetic variability in its metabolism and drug or dietary interactions.^{2,3} VKA have a narrow therapeutic window

leading to inconvenient frequent monitoring.^{2,3} In addition, they also carry a significant risk for hemorrhagic complications.⁴

Since 2010, several direct acting oral anticoagulants (DOAC) have been approved for use in patients with VTE and nonvalvular AF. These agents have overcome several of the limitations associated with VKA; in that, they have faster onset of action (0.5–4 h), shorter half lives (12–17 h), fewer food and drug interactions, and no need for coagulation monitoring.³ These differences may translate into similar efficacy with greater ease of administration and lower bleeding risk. This

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review focuses on the current indication of DOACs along with process of choosing the appropriate drug for patients with nonvalvular AF and VTE.

Classification of DOAC

There are a lot of acronyms in use for this new class of anticoagulants. These acronyms include direct oral anticoagulants (DOACs), target-specific oral anticoagulants (TSOACs), oral direct inhibitors (ODIs), and novel oral anticoagulants (NOACs). The International Society on Thrombosis and Haemostasis (ISTH) in their 2015 recommendation statement has suggested the usage of DOAC as acronym for these agents. The earlier most widely used acronym for these agents, NOAC, has some safety limitations; in that, in some instances, it has been interpreted as “No oral anticoagulation”. The use of acronym DOAC for this class of anticoagulants should be encouraged. Two classes of DOACs are currently available, the oral direct thrombin inhibitors (dabigatran) and actor Xa inhibitors (rivaroxaban, apixaban, and edoxaban). Unlike VKAs, these drugs block the activity of one single step in coagulation cascade. The pharmacokinetic and pharmacodynamic properties of the DOAC are as given in Table 1.

Dabigatran etexilate a direct thrombin inhibitor was the first DOAC studied and approved by FDA based on the results of the RE-LY (Randomized Evaluation of Long-term anticoagulant therapy with dabigatran etexilate) trial.⁵ Dabigatran capsules should be kept away from moisture as this can lead to product breakdown and loss of potency. The capsules should not be crushed or opened before administration as this can result in dramatic increases in oral bioavailability.⁶ **Rivaroxaban** is a competitive and dose-dependent direct inhibitor of factor Xa. It was approved by the FDA based on the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of

Stroke and Embolism Trial in AF).^{7,8} **Apixaban** is a direct, reversible, competitive, and selective inhibitor of factor Xa.^{9,10} It is predominantly metabolized by the liver. Rivaroxaban and apixaban are contraindicated for use along with drugs capable of inducing or inhibiting CYP3A4.¹⁰ **Edoxaban** is another reversible factor Xa inhibitor.¹¹ The drug is a substrate for P-glycoprotein; hence concomitant use of potent glycoprotein inhibitors (verapamil or quinidine) will require dose modification as these drugs will raise the drug levels of Edoxaban.¹² The indications, dosage, and contraindications for DOACs are as given in Table 2. The choice of DOAC in a given clinical situation is as given in Table 3.

Summary of DOAC trials

Summary of the major clinical trials of DOACs is as given in Table 4.^{5,7,10,12} Clinical trial data with DOAC showed a similar or lower incidence of major bleeding compared with Warfarin. The risk of intracranial hemorrhage (ICH) was 33–70% lower in patients treated with a DOAC. The rate of fatal bleeding was lower in patients treated with apixaban, rivaroxaban, edoxaban, and low-dose (110 mg bid) dabigatran compared with patients treated with Warfarin. However, a similar rate of fatal bleeding was seen in patients treated with high-dose (150 mg bid) dabigatran.⁵ The incidence of major gastrointestinal (GI) bleeding was lower with low-dose (30 mg od) edoxaban group¹²; apixaban and low-dose dabigatran (110 mg bid) groups; while it was higher in patients treated with high-dose (150 mg bid) dabigatran, rivaroxaban, or high-dose edoxaban (60 mg od). Dabigatran-treated patients had a significantly greater incidence of dyspepsia compared with Warfarin-treated patients.⁵

Meta-analysis of these trials (RE-LY,⁵ ROCKET AF,⁷ ARISTOTLE,¹⁰ ENGAGE AF-TIMI¹²) as a group compared to dose adjusted Warfarin was associated with a reduction in all-cause mortality (RR 0.90, 95% CI 0.85–0.95, $P = 0.0003$).¹³ DOACs

Table 1 – Comparison of Warfarin with direct oral anticoagulants.

Characteristics	Warfarin	Apixaban	Dabigatran	Rivaroxaban	Edoxaban
Bioavailability	95%	<50% for 10 mg dose	6%	66% without food up to 100% with food	<60% for 60 mg dose
Time to peak activity	48–96 h	3–4 h	0.5–2 h	2.0–4 h	1–2 h
Half life	20–60 h	<12 h	11–14 h	6–12 h, slightly prolonged in elderly	6–11 h
Dosing frequency	Once daily	Twice daily	Twice daily	Once daily	Once daily
Drug interactions	Strong inducers and inhibitors of CYP3A4 and P-gp	Strong inducers and inhibitors of CYP3A4 and P-gp	Strong inducers and inhibitors of P-gp	Strong inducers and inhibitors of CYP3A4 and P-gp	Strong P-gp inhibitor
Renal elimination	<5%	<25%	85%	35%	<50%
Hepatic elimination	Yes	Yes	No	Yes	No
Laboratory measurement of anticoagulant effect	PT (INR)	Anti-factor Xa assay,	aPTT or TT,	Anti-factor Xa assay	Anti-factor Xa assay,
Reversal agent	Available (Vit K)	Under trial	Idarucizumab	Under trial	Under trial
Procoagulant used	FFP	PCC	aPCC	PCC	PCC

CYP, cytochrome P450; P-gp, P-glycoprotein; PT, prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; aPCC, activated prothrombin complex concentrate.

Table 2 – Clinical indications, dosage and contraindications of direct acting oral anticoagulants.

	Dabigatran	Apixaban	Rivaroxaban
<i>Clinical indication</i>			
Atrial fibrillation	150 mg or 110 mg twice daily	5 mg twice daily ^b	20 mg daily ^a
Acute pulmonary embolism (PE) as single agent	Not approved ^c	10 mg twice daily for initial 7 days, 5 mg twice daily thereafter	15 mg twice daily for initial 21 days 20 mg daily thereafter,
Acute and chronic deep venous thrombosis (DVT)	150 mg twice daily	5 mg twice daily	20 mg daily
Prevention of venous thrombo embolism after knee or hip replacement surgery	110 mg (initial dose) then 220 mg daily	2.5 mg twice daily	10 mg daily
<i>Contraindications</i>	Clinically significant bleeding Hepatic impairment CrCl <15 ml/min Prosthetic heart valves requiring anticoagulation Concurrent administration of ticagrelor or prasugrel	Clinically significant bleeding Hepatic impairment CrCl <30 ml/min Prosthetic heart valves requiring anticoagulation Concurrent administration of ticagrelor or prasugrel	Clinically significant bleeding Hepatic impairment CrCl <15 ml/min Prosthetic heart valves requiring anticoagulation Concurrent administration of ticagrelor or prasugrel Pregnancy or breastfeeding

^a Dose should be 15 mg daily if estimated glomerular filtration rate is <50 ml/min.
^b Dose should be 2.5 mg twice daily if 2 out of these 3 criteria are present: creatinine level ≥133 µmol/L; age ≥80 yrs; weight ≤60 kg.
^c Dabigatran approved for used in pulmonary embolism only in combination with heparin.
CrCl, creatinine clearance.

Table 3 – Suggested use of direct acting oral anticoagulants according to patient characteristics.

Patient characteristic	DOAC regimen advised	Remarks
Patients with AF (atrial fibrillation) with, CHADS2 score ≥3 or previous history of stroke	Dabigatran, 150 mg twice daily	Dabigatran noted to have the greatest risk reduction for stroke compared with Warfarin
Patients of AF with high risk of bleeding	Apixaban, 5 mg twice daily	Apixaban noted to provided the greatest risk reduction of major bleeding compared with Warfarin
	Dabigatran, 110 mg twice daily	Risk of major bleeding lower with reduced dosage of dabigatran compared with Warfarin
Patients with AF and venous thrombo embolism and dyspepsia or other gastrointestinal complaints	Apixaban or rivaroxaban	Less dyspepsia noted with these drugs compared to dabigatran
Patients of AF with poor compliance of medication	Rivaroxaban, 20 mg daily	Once-daily dose allows better compliance
Elderly (≥80 yrs) patients with renal dysfunction (eg, eGFR < 50 ml/min)	Apixaban, 2.5 mg twice daily	Apixaban noted to have least bleeding risk in patients with renal dysfunction.
CHADS2, congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, and stroke or transient ischemic attack; eGFR, estimated glomerular filtration; DOAC, direct acting oral anticoagulant.		

significantly reduce the incidence of all stroke (ischemic or hemorrhagic stroke) and systemic embolism by 19%.¹³ There was a non-significant reduction in the incidence of ischemic strokes and the benefit was mainly driven by a 51% reduction in hemorrhagic strokes.¹³ Subgroup analysis revealed no significant difference in the incidence of stroke or systemic embolism in the subgroups stratified by: age; sex; diabetes; renal impairment; history of stroke; CHADS2-score; or adequacy of anticoagulation with VKA.¹³ A greater relative reduction in major bleeding complications was noted with DOAC therapy compared to Warfarin when the time in the therapeutic range was <66% (RR 0.69 vs. 0.93, $P = 0.022$).¹³ This suggested that efficacy and safety of DOACs were noted irrespective of how good Warfarin therapy was managed.¹³ In contradistinction to this, the meta-analysis by Gómez-Outes et al. found the benefit of DOAC in only lowering the risk of intra cranial bleeding.¹⁴ They did not find these agents to be

superior to VKA in preventing ischemic strokes and systemic embolic events (SEE). The superiority of DOAC over VKA in the composite of all strokes and SEE in the RE-LY⁵ and ARISTOTLE¹⁰ study was mainly driven by the results from the Non-European countries.¹⁴ This geographical difference in the results could have resulted from either poor quality of the oral anticoagulation or poor control of the risk factors for thrombosis in the Non-European countries.¹⁴ DOAC certainly hold promise in subset of patients where the quality of anticoagulation is poor.

Comparison of various DOACs

There are no trials with head-to-head comparison of various DOACs. Clinical trial data show that all DOACs provide equal or greater protection against all-cause strokes as compared to

Table 4 – Major clinical trial of direct acting oral anticoagulants.

	ARISTOTLE ¹⁰	RE-LY ⁵	ENGAGE AF-TIMI ¹²	ROCKET AF ⁷
Study drug	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Comparator	Warfarin	Warfarin	Warfarin	Warfarin
Doses studied	5 mg bid	150 mg bid	60 mg od	20 mg od
Number of risk factors	≥1	≥1	≥1	≥2
Number of patients	18,201	18,113	21,105	14,264
Mean CHADS2 score	2.1 vs. 2.1	2.2 vs. 2.1	2.8 vs. 2.8	3.5 vs. 3.5
Stroke or systemic embolism	1.27% vs. 1.60% per year (P = 0.01)	1.11% vs. 1.69% per year (P < 0.001)	1.18% vs. 1.50% per year (P < 0.001)	1.7% vs. 2.2% per year (P < 0.001)
Major bleeding	2.13% vs. 3.09% per year (P < 0.001)	3.11% vs. 3.36% per year (P < 0.001)	2.75% vs. 3.43% per year (P < 0.001)	14.9% vs. 14.5% per year 9 (P = 0.44)
Intracranial bleeding	0.33% vs. 0.80%; (P < 0.001)	1.45% vs. 1.80% per year (P = 0.04)	0.39% vs. 0.85% per year; (P < 0.001)	0.5% vs. 0.7% per year (P = 0.003)
Gastrointestinal bleeding	0.76% vs. 0.86% per year (P = 0.37)	1.51% vs. 1.02% per year (P < 0.001)	1.51% vs. 1.23% per year (P = 0.03)	3.15% vs. 2.16% per year; (P < 0.001)

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-Thrombolysis In Myocardial Infarction Study 48; RE-LY, Randomized Evaluation of Long-term anticoagulation therapy; ROCKET AF, Rivaroxaban Once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation; CrCl, creatinine clearance; CHADS₂, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, and Stroke or TIA previous event (2 points).

dose adjusted Warfarin; a benefit driven primarily by reduction of hemorrhagic strokes. Dabigatran appears to be more promising in terms of preventing ischemic stroke as compared to Warfarin.^{5,13} All DOACs appear to have a more favorable safety profile compared to Warfarin in reducing ICHs.^{5,7,10,13} Most of the DOACs except for apixaban have been noted to have an increased risk for GI hemorrhages. Apixaban is preferred in patients with severe renal dysfunction.

Advantages of DOAC over VKA use

VKA have narrow therapeutic window with a variable dose-response relationship to variety of factors. DOACs unlike VKA do not require dietary restrictions of Vitamin K rich foods.⁴ DOACs are absorbed readily and have quick onset of action compared to VKA and hence do not require bridging with other form of anticoagulants. In the background of shorter half life, these agents have quick offset of anticoagulant effect. DOACs have fewer drug-drug interactions which makes them more suitable option for many patients with AF who require multiple concomitant medications.¹⁵ Fewer dietary and drug-drug interactions of these agent's result in a relatively steady state plasma concentration thereby leading to lesser fluctuation in the anticoagulation effect; hence obviating the need for frequent and regular laboratory monitoring.^{4,13}

Clinical conditions where VKAs may be preferred

VKA are preferably used in patients who have excellent stable INR control as one gains very little by switching over to DOACs. However, DOACs are contraindicated in the following clinical situations.¹⁵

- Prosthetic heart valves – DOACs are associated with greater risk of valve thrombosis hence not used in these patients.

- Pregnancy – Because of lack of clinical experience DOACs are not used during pregnancy. Unfractionated or low molecular weight heparin is preferred in most pregnant women.
- Renal impairment – DOACs are excreted by kidneys to variable degrees; hence VKA are used in patients with renal impairment.
- Antiphospholipid syndrome (APS) – Data on the efficacy of DOAC in the setting of APS who require anticoagulation are not available; hence heparin followed by VKA is generally the preferred therapy.
- Compliance – Apixaban and dabigatran require twice daily dosing; this in the background of short half live mandates good compliance with medication. Missing one or two doses of these agents can lead to inadequate anticoagulation. Patients where drug compliance is not assured, VKA are preferred because of their longer half lives.
- GI disease – In patients with GI diseases (history of bleeding, severe dyspepsia) dabigatran is contraindicated as the drug is associated with higher incidence of dyspepsia and GI bleeding.
- Cost – In a poor country like India, cost is an important factor as DOACs are expensive; hence if adequate anticoagulation is achieved with VKA then these are the preferred agents because of low cost of therapy.

Clinical scenarios

Bleeding on DOAC

Bleeding is considered a major drawback for the use of DOAC. Bleeding episodes in patients on DOAC may be either mild, moderate to severe or life threatening. Supportive measures take the center stage during the bleeding episode and include hemodynamic support, mechanical compression and surgical intervention if required.^{16,17} The management strategy for patients while on DOAC is as given in Fig. 1. As these drugs

Management of bleeding with DOAC

Fig. 1 – Management strategy for patients with bleeding while on direct acting oral anticoagulants.

have a short half-life, mere stopping the drug is good enough in patients with mild bleeding with normal renal function. Volume resuscitation with fluids and blood components along with local hemostasis of the source of bleeding is required in those with moderate to severe bleeding. Hemodialysis though difficult in actively bleeding patient may be effective in patients taking dabigatran but not so in patients on Xa inhibitors. Patients with life-threatening bleeding require immediate hemodynamic and hemostatic resuscitation. Prothrombin complex concentrate (PCC) or activated prothrombin complex concentrates (aPCC) may be used in these patients. Activated PCC is more effective in patients on dabigatran. PCC is administered in the dosage of 25 U/kg and can be repeated if clinically indicated. Activated PCC if available is started in the dosage of 50 IE/kg (maximum 200 IE/kg/day).⁴ Use of recombinant activated factor VIIa (rVIIa) in patients on DOAC is still controversial as there are no human studies available. Unlike in bleeding with VKA, fresh frozen plasma (FFP) has no role in management of patients bleeding while on DOAC as these patients do not have deficiency of clotting factors. Specific antidotes are now available and should be used, and detailed account of the same is given in the section of DOAC reversal. A recent meta-analysis showed that the patients on dabigatran had a shorter hospital stay and a lower adjusted all-cause mortality at 30 days compared to Warfarin following major bleeding episode.¹⁶

DOAC reversal

The need for reversal agent for DOAC is rare due to rapid offset of their action; however, reversal agent is required in small group of patients with life-threatening bleeds or those undergoing emergency surgery. Idarucizumab, a monoclonal antibody fragment with 350 times higher affinity to bind dabigatran, has recently been approved by FDA for use in patients on dabigatran.¹⁸ It neutralizes the activity of dabigatran by binding to both the free and thrombin-bound dabigatran. It is administered in the dose of two 50-ml bolus infusions each containing 2.5 g of idarucizumab.¹⁸ In the interim report of ongoing trial (RE-VERSE AD) drug was well tolerated with no safety concerns among the 90 patients

studied.¹⁹ There was complete reversal of anticoagulant activity in 90% of patients.¹⁹ Andexanet alfa a recombinant modified Factor Xa reversal agent neutralizes both direct and indirect Factor Xa inhibitors (rivaroxaban, apixaban and edoxaban; LMWH and fondaparinux).²⁰ Once bound with andexanet alfa the Factor Xa inhibitors are unable to bind to native Factor Xa thereby allowing restoration of normal hemostatic processes. The drug is currently undergoing phase 3 trials.²⁰

Monitoring of patient on DOAC

Baseline checks on the platelet count, activated partial thromboplastin time (aPTT), International normalized ratio (INR), and renal functions is mandatory before starting any patient on DOAC. While a patient is on DOAC one needs to check for compliance for medication and tolerance. The effect of dabigatran is more marked on aPTT than prothrombin time (PT). aPTT however cannot be used to quantify the drug plasma concentration as the dose response is not linear. A prolonged aPTT is not strongly predictive of hemorrhage and patients may experience bleeding while displaying a normal aPTT.²¹ Among the specific tests, a thrombin time (TT) is considered too sensitive toward dabigatran, and hence a diluted thrombin time (dTT) is used to calculate the plasma concentrations of dabigatran.²¹ A normal TT suggests very low levels of dabigatran. Factor Xa inhibitors prolong both aPTT and PT, the latter being more sensitive to the effects of direct Xa inhibitors. Rivaroxaban has more pronounced effect on PT and aPTT than apixaban.²¹ These tests can be used to determine the relative intensity of anticoagulation but should not be used to quantify drug plasma concentrations. Anti Xa chromogenic assays using validated calibrators could be used to measure the plasma concentration of factor Xa inhibitors.²¹

However, in contrast to VKA, routine laboratory testing with aPTT and PT is not used to determine the anticoagulant efficacy of DOAC.²¹ These tests have a lot of inter-lot variability and more importantly are not widely available. It is important to impress on the patients that adherence to treatment is essential for maintaining anticoagulation as these drugs have short half-life and rapid offset of action.

Table 5 – Recommendation on how to switch between different anticoagulant regimens.

Switching	Suggested protocol
VKA to DOAC (direct acting oral anticoagulant)	Discontinue VKA and start DOAC once INR (international normalized ratio) is below 2.0
Intravenous unfractionated heparin (UFH) to DOAC	Start the DOAC 2 h after stopping UHF (longer in patients with renal dysfunction)
Low-molecular-weight heparin (LMWH) to DOAC	DOAC to be given whenever the next dose of LMWH is due
DOAC to VKA	Concomitant treatment with both drugs; duration of overlap is determined by renal function. UHF may be required after stopping DOAC till INR is optimized. Factor Xa inhibitors prolong the INR hence monitoring may be difficult.
DOAC to parenteral anticoagulant (UFH, LMWH)	Start UHF or LMWH whenever the next dose of DOAC is due
One DOAC to another	Switch over from one DOAC to another as per the pharmacokinetics of the drug chosen; modify the dosage as per renal function.

Thromboembolic complications with DOACs

There is fast offset of the anticoagulant effect of DOAC drugs due to its short half life which leads to therapeutic gap during transition from DOAC to VKA predisposing patients to thromboembolic complications. This was observed during transition from Warfarin to rivaroxaban in the ROCKET – AF trial.²² In view of this sudden discontinuation of these agents is contraindicated except when one encounters hemorrhagic complications. A strict protocol of switching over from DOAC to VKA or heparin should be followed to prevent this complication.²² Various bridging protocols for switching from one anticoagulant to the other are given in Table 5.

DOAC use in the elderly

Dabigatran and Rivaroxaban were noted to have increased risk of major extra cranial bleeds with increasing age.^{5,13,23} Major bleeding complications while on DOAC were encountered more frequently in patients older than 80 years.¹³ Dosage reduction of dabigatran (110 mg BD) and Apixaban (2.5 mg BD) is recommended for patients >80 years. Dosage modification is also recommended in elderly with co-morbid condition and concomitant drugs which increase the risk of bleeding.

DOAC in patients with renal function

Renal function dictates the dosage modification of DOAC. These drugs are best avoided in patients with severe renal insufficiency (creatinine clearance below 30 ml/min). Dosage

modification is recommended in patients with creatinine clearance between 30 and 50 ml/min (dabigatran 110 mg BD, Rivaroxaban 15 mg OD, Apixaban 2.5 mg BD). Among all the available DOAC's, Apixaban is considered to be the safest. VKA is preferred in patients with severe renal dysfunction.

DOAC in patients at risk for ischemic stroke

The risk of stroke in patients with nonvalvular AF depends on the associated risk factors (congestive heart failure, hypertension, age, diabetes mellitus, and prior stroke/transient ischemic attack) integrated in a tool called CHADS₂. This risk score has been further supplemented the addition of other risk factors as vascular disease, age (65–74 yrs), and female sex. This new tool is called CHA₂DS₂-VASc and is recommended to be used for patients with CHADS₂ score <2. There is a linear relation of increase in incidence of stroke with increasing risk score. OACs are recommended as per European Society of Cardiology (ESC) guidelines²⁴ for patients with a CHADS₂ score ≥2 or CHA₂DS₂-VASc score of 1. Patients with high stroke risk (CHADS₂ ≥3) were noted to have more benefit with the usage of DOACs over VKA.¹³ The intensity of the anticoagulant therapy is going to be dictated by the balance of CHADS₂-VASc score and bleeding risk.²⁴ In patients with high bleeding risk the lower tested dose of DOAC (dabigatran 110 mg bid, rivaroxaban 15 mg od or apixaban 2.5 mg bid) may be used. The benefit of DOAC over VKA was not much in patients at low risk of stroke (CHADS₂ score >1); hence VKA remains a viable alternative to DOACs in these subjects. This is particularly important in a developing country like India, where the cost of therapy matters.

DOACs and antiplatelet agents

Approximately 20–30% of patients with AF have significant coronary artery disease while 5% of patients undergoing percutaneous coronary intervention have associated AF.²⁵ These patients require combination of anticoagulants and antiplatelet drugs. Clopidogrel is combined with aspirin and VKA as part of triple therapy. Concomitant use of oral anticoagulant and dual antiplatelet therapy is associated with 2–3 folds' increase in the risk of bleeding. In view of elevated risk of bleeding in combination with antiplatelets, a lower intensity of anticoagulation is recommended with VKAs (INR of 2.0–2.5) or DOAC (apixaban 2.5 mg bid, rivaroxaban 15 mg od, dabigatran 110 mg bid).²⁵ In RE-LY trial, concomitant use of dual antiplatelet therapy with dabigatran was associated with increased risk of major bleeding (HR 2.31, 95% CI 1.79–2.98).⁵ In the first ever randomized comparison of VKA vs. DOAC along with antiplatelets in patients with nonvalvular AF undergoing PCI, the PIONEER AF-PCI study, assessed the relative risk of bleeding at 1 year follow-up.²⁶ In this trial 2, rivaroxaban treatment strategies (rivaroxaban 15 mg once daily plus clopidogrel 75 mg daily or rivaroxaban 2.5 mg twice daily with DAPT) and 1 VKA treatment strategy (VKA plus DAPT) were tested. At the end of 1 year, both the rivaroxaban treatment strategies had lower bleeding risk compared to the standard VKA strategy. All the 3 groups had similar rates of death from

Table 6 – Pre- and postoperative management of patients taking direct acting oral anticoagulants based on creatinine clearance.

Creatinine clearance ml/min		Minor surgery	Major surgery
Dabigatran	>50	Stop 48 h before surgery and restart 24 h after surgery	Stop 72 h before surgery and restart 48 h after surgery
	30–50	Stop 72 h before surgery and restart 24 h after surgery	Stop 72 h before surgery and restart 48 h after surgery
Apixaban	>30	Stop 48 h before surgery and restart 24 h after surgery	Stop 72 h before surgery and restart 48 h after surgery
Rivaroxaban	>30	Stop 48 h before surgery and restart 24 h after surgery	Stop 72 h before surgery and restart 48 h after surgery

cardiovascular events, myocardial infarction, or stroke.²⁶ The limitation of the trial was that it was underpowered to detect the difference of stroke rate, and one would not be sure if rivaroxaban in the dose of 2.5 mg BD along with antiplatelet therapy will be sufficient to prevent stroke.

Aspirin when used with DOAC is recommended in the dose of 75–100 mg/day. In patients at high risk of bleeding dual therapy (VKA/DOAC along with single antiplatelet agent) is used. As on date the combination of DOAC with either ticagrelor or prasugrel is contraindicated as the same has not been tested in clinical trials.²⁵ Proton pump inhibitors are recommended to be used to minimize the risk of GI bleeding. After one year of angioplasty all the patients are continued on VKA/DOAC as a single agent. Antithrombotic therapy is also tailored based on the clinical setting (acute coronary syndrome vs. chronic stable angina), stroke or the bleeding risk and type of stent used (drug eluting vs. bare metal stent). Newer-generation drug-eluting stents are preferred especially in patients at a high risk of bleeding as they require shorter duration of dual antiplatelet therapy.^{24,25}

DOACs protocol during perioperative period

The management of anticoagulation in the perioperative period is primarily governed by the patient characteristic particularly renal function, type of surgery (major or minor) and the anesthetic regimen used. Different preoperative protocols used in these patients while on DOAC are as given in Table 6. As a rule in surgeries with high bleeding risk, the DOAC need to be discontinued 3 days prior to surgery and restarted 48 h post surgery.²⁷

Concomitant thrombolysis and DOACs in patients with acute ischemic stroke

Routine administration of systemic thrombolytic agents is not recommended in patients who are on DOACs due to high risk of bleeding. As there are no reliable tests available to measure the anticoagulant effect of DOAC, the timing of last dose gives an indication of the potential anticoagulant effect of these drugs.²⁸ Even when the coagulation parameters are normal, a great degree of caution needs to be exercised while considering concomitant thrombolytic therapy.²⁸ Continuation or discontinuation of the DOAC after stroke is going to be dictated by the severity of the stroke. As per the recommendations of

European heart rhythm association the initiation of anticoagulation in patients of AF with ischemic stroke is based on what is known as the '1-3-6-12 day rule'. According to this rule oral anticoagulation following the event can be initiated in patients with transient ischemic attack, mild stroke National Institute of Health Stroke Scale (NIHSS <8), moderate stroke (NIHSS 8–16) and in severe stroke (NIHSS >16) at 1, 3, 6 and 12 days respectively.^{24,28,29} Stroke while on DOAC mandates looking for an alternate cause (large vessel disease, dissection, etc.).

DOAC protocol for cardioversion in patients with AF

Thrombo-prophylaxis is required for both pharmacological and electrical cardioversion in patients with AF. The risk of thromboembolism without adequate anticoagulation is 5–7%. OAC therapy is recommended for at least 3 weeks prior and 4 weeks following cardioversion in patients with AF of more than 48 h duration.^{24,30} Anticoagulation can be omitted if AF is less than 48 h duration or no LA clot is demonstrated on trans esophageal echocardiography. Analysis of major trials suggests that DOACs may be as effective as VKAs when used for this indication.^{30,31} In the X-VerT study rivaroxaban was noted to be a safe and effective alternative to VKAs in patients of AF undergoing cardioversion.³¹

Conclusion

DOACs represent an appealing alternative to VKA for prevention of stroke in patients with nonvalvular AF and treatment or prevention of VTE. These drugs are safer and more efficacious compared to VKA. As a group, they have rapid onset of action, shorter half life, fewer drug or food interactions, and do not require monitoring of anticoagulant efficacy. Bleeding risk with the exception of GI bleeding is lower with these agents. While starting these drugs patient's age and renal function should be taken into consideration. Recent FDA approval of antidote for dabigatran and ongoing clinical trials of antidotes for other agents has further strengthened the safety for these agents.

Conflicts of interest

The authors have none to declare.

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