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# Non-Vitamin K Antagonist Oral Anticoagulants in Atrial Fibrillation


## ABSTRACT

Atrial Fibrillation (AF) is the most common supraventricular tachycardia resulting in hospitalization and morbidity. Patients with AF are anticoagulated to reduce stroke risk. However, the majority of them are not properly anticoagulated or not treated. Vitamin K antagonist were developed mainly to reduce the patient's clotting risk but required therapeutic monitoring and had multiple drug interactions. Many studies have found Non-Vitamin K Antagonist Oral Anticoagulants (NOACs) to be as effective as Warfarin in reducing stroke and embolism by reducing intracranial bleed. Hence, this article explores the physician's reason for under treatment and focusing on the role of NOACs as per indications. The first step in all AF patients is to see whether AF is valvular or non-valvular. If valvular than only Vitamin K antagonist Oral Anticoagulants can be used and if non-valvular NOACs can be used. In the present article we review the role of different NOACs in the management of non-valvular AF (NVAF) and their antidotes. We also focus on when, where, and how long NOACs to be given. Latest guidelines also recommend increased NOAC use in NVAF mainly to reduce or prevent mortality and morbidity.


**Key words:** Atrial fibrillation, Non-Vitamin K antagonist oral anticoagulants, NOAC and AF

## INTRODUCTION

Atrial fibrillation (AF) is the most common supraventricular tachyarrhythmia (hazard ratio (HR): 300–600 beats/min) encountered in clinical practice, characterized by electrocardiographically by low-amplitude baseline oscillations and an irregularly irregular ventricular rhythm lasting for 30 s. The prevalence of AF increases with age and more in the male population.[1] Over a span of two decades, there was a steady but modest increase in the prevalence rates –596.2 in men and 373.1 in women per 1,00,000 population, while the incidence rates significantly increased to 77.5 and 59.5 in men and women, respectively.[2] This prevalence varies between a low 0.4% in age group of 55 and 60 years old to 15% in those above 85 years.[2] AF is classified as valvular AF (VAF) if the AF occurs in the presence of moderate-to-severe mitral stenosis or a mechanical prosthetic valve. Rest AF are non-VAF (NVAF)[3] now recently classified into evaluated heart valves rheumatic or artificial European heart rhythm association (EHRA) Type 1 and 2 [Table 1].[4]

Incidence of cerebrovascular accidents (CVA) increases by 4.0-fold in men and 5.7-fold in women in the presence of AF. It also increases the risk of heart failure by about 3.0-fold in men and about 11.0-fold in women by affecting the atrial contribution to ventricular filling, while dementia is also increased about 1.4-fold[5-7] AF also increases all-cause mortality (ACM) by about 2.4-fold in men and about 3.5-fold in women.[8] AF does not increase incidence and prevalence but increases risk of mortality and morbidity. Patients with hypertension, ischemic heart disease, valvular heart disease, cardiomyopathy, constrictive pericarditis, and pulmonary hypertension are prone to AF. AF is classified into paroxysmal, early persistent, long-standing persistent, and permanent [Table 2]. Permanent AF is labeled when the patient and clinician jointly decide to abandon further attempts at restoring and/or maintaining sinus rhythm (Therapeutic Attitude).[9]

It has been shown that aspirin decreases the incidence of CVA in AF patients by about 19%, while warfarin showed a decrease in CVA by about 62%.[10] Warfarin acts indirectly by inhibiting Vitamin K-dependent coagulation Factors II, VII, IX, and X that are needed in clot formation.[10] Newer agents that directly inhibit coagulant factors include the direct thrombin inhibitors (DTI)-dabigatran and ximelagatran, the factor Xa inhibitors-rivaroxaban, apixaban, edoxaban, and betrixaban and the even newer factor XIa inhibitor asundexian. Why to change over to Non-Vitamin K Antagonist Oral Anticoagulants (NOAC). First, there is conclusive evidence that hemorrhagic strokes and intracranial bleedings are much fewer in number with NOACs than with warfarin. The risk of intracranial bleeding is 52% lower with NOACS than with warfarin, with extremes ranging from 33 to 70%[11] irrespective of time-in-


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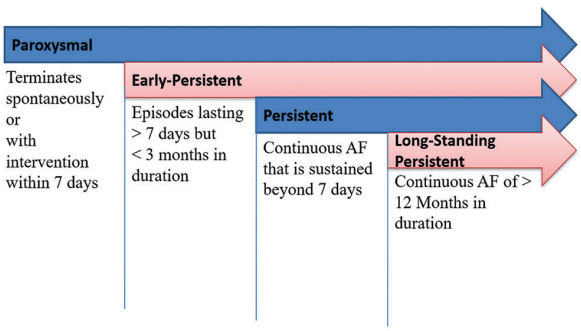
**Table 1:** Atrial Fibrillation and "Valvular Heart Disease"

| Definition | Valvular heart disease |
|---|---|
| EHRA type 1 VHD AF patients with "VHD needing therapy with a Vitamin K antagonist (VKA)" | • Mitral stenosis (moderate-severe, of rheumatic origin)<br>• Mechanical prosthetic valve replacement<br>• Mitral regurgitation<br>• Mitral valve repair |
| EHRA type 2 VHD AF patients with "VHD needing therapy with a VKA or an NOAC," also taking into consideration $CHA_2$-$DS_2$-VASc score risk factor components | • Aortic stenosis<br>• Aortic regurgitation<br>• Tricuspid regurgitation<br>• Tricuspid stenosis<br>• Pulmonary regurgitation<br>• Pulmonic stenosis<br>• Bioprosthetic valve replacements<br>• Trans-aortic valve intervention |

$CHA_2$-$DS_2$-VASc: Congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled) – Vascular disease, age 65–74 and sex category (female); EHRA: Evaluated Heart Valves, Rheumatic or Artificial; VHD: Valvular heart disease.

**Table 2:** Types of AF




therapeutic range under warfarin (renal dysfunction, or prior stroke or intracranial bleeding), less drug interactions, cost, frequent International Normalized Ratio (INR) monitoring, and unpredictable onset and offset.

The general question that arises in the presence of AF is whether an oral anticoagulant (OAC) is needed in all patients of AF or only in a selected. If yes than how long? Initiating treatment depends on severity and frequency of Symptoms, hemodynamic effect, duration, frequency, burden of AF, left atrium size, heart failure, current antiarrhythmic drugs, risk of Stroke, underlying heart disease or comorbidities.

Risk stratification for stroke and bleeding is done using $CHA_2DS_2$-Vasc score and HASBLED score, respectively [Table 3].

## DO ALL AF PATIENTS NEED AN OAC?

Management of AF has changed from confirm, characterize to anticoagulate, better symptom control, and cardiovascular risk control. The first step is to see whether there is a significant valvular disease (moderate-to-severe mitral stenosis or a mechanical cardiac prosthetic valve). If there is VAF, then only VKA OAC must be used. This has been recently confirmed in the INVICTUS trial presented at ESC 2022, where VKA was more effective than rivaroxaban in such patients.[12]

**Table 3:** $CHA_2Ds_2$VASc Scoring System and adjusted stroke rate (%/year)

| Risk factor | Score |
|---|---|
| CHF/LVEF ≤0.4 | 1 |
| Hypertension | 1 |
| Age ≥75 | 2 |
| Diabetes | 1 |
| Storke/TIA/Thromboembolism | 2 |
| Vascular disease | 1 |
| Age 65–74 | 1 |
| Female | 1 |
| $CHA_2$ $DS_2$ VASC score | Stroke Risk (%/year) |
| 0 | 0 |
| 1 | 1.3 |
| 2 | 2.2 |
| 3 | 3.2 |
| 4 | 4 |
| 5 | 6.7 |
| 6 | 9.8 |
| 7 | 9.6 |
| 8 | 6.7 |
| 9 | 15.2 |

Once NVAF is established, then calculate $CHA_2DS_2$VASc score and HAS-BLED score.

- If the $CHA_2DS_2$VASc is one in male and two in female based patients characteristics and individual preferences to prevent thromboembolism (class II a). If the $CHA_2DS_2$VASc is >2 in men or >3 in women, then NOAC is recommended (class I).
- If the $CHA_2DS_2$VASc score is >2, but the HAS-BLED is 2–3 (high bleeding risk), then consider must be given to left atrial appendage occlusion (LAAO) using a suitable device.[13]

Once a decision is taken to use an OAC, the question becomes which one should be used.

## VKAS AND NON-VKAS

As VKA (mainly warfarin) has been shown to reduce the risk of CVA by about 62%, it became the standard of care, and aspirin was used only in patients who had a very high bleeding risk. Various trials were done comparing warfarin with the NOACs dabigatran, rivaroxaban, apixaban, and edoxaban in various trials as enumerated below.

The randomized evaluation of long-term anticoagulation Therapy trial published in 2009 where in 18,113 patients with AF, warfarin was compared to dabigatran in a dose of

110 mg twice a day or 150 mg twice a day. The mean follow-up period was 2 years and mean $CHADS_2$ score was 2.1. The primary endpoint of this trial was CVA/STE was non-inferior for dabigatran in the dose of 110 mg twice a day (HR 0.9, 95% CI 0.74–1.1) and superior when dabigatran was used in a dose of 150 mg twice a day (HR 0.66, 95% CI–0.74 0.82). Higher dose was associated with increased hemorrhagic stroke.[14]

The next trial was the ROCKET-AF trial published in 2011. 14,264 patients, rivaroxaban was compared to warfarin in patients with AF. In the rivaroxaban group, the median age was 73 years, 40% were women, mean $CHADS_2$ score was 3.5, 40% had diabetes, mean blood pressure was 130/80 mm Hg, and 55% had prior stroke, TIA, or systemic embolism and mean follow-up period was 1.9 years. The ACM was reduced with rivaroxaban (HR-0.85) as was ischemic CVA (HR-0.94) and hemorrhagic CVA (HR 0.59).[15]

The ARISTOTLE trial published in 2011. Here in 18,201 patients, apixaban was compared to warfarin in patients with AF. The mean follow-up period was 1.8 years. The ACM was reduced with apixaban (HR-0.89) as was ischemic CVA (HR-0.92), and hemorrhagic CVA (HR-0.51) with a significant reduction in ICH (HR 0.61).[16] Apixaban had an even greater safety profile among patients whom most clinicians would consider at higher risk from apixaban – those with low body weight and impaired renal function and few GI bleeding as compared to Dabigatran.

The last trial was ENGAGE-TIMI-48 published in 2013.[17] Here 21,105 edoxaban in two doses of 30 mg and 60 mg once a day was compared to warfarin in patients with AF. The mean follow-up period was 2.8 years. Both doses were non-inferior to warfarin in preventing CVA/STE. The hemorrhage was similar to warfarin with 30 mg but more with 60 mg. Here also the ICH was lesser compared to warfarin, while the ACM was similar.

Considering all the available data as enumerated above – it is now a standard practice to use a NOAC in patients with AF who are considered candidates for an OAC.

## CLINICAL PHARMALOGY NOACS

### Dabigatran

Dabigatran is DTI that directly inhibits factor II with half-life of about 15 h. Around 85% of the drug is excreted unchanged in the urine. Kidney function test and liver function test should be assessed before starting Dabigatran and then annually. The usual dose is 150 mg twice daily. However, it can be used in a reduced dose of 110 mg twice daily if the patient is above 80 years or if the glomerular filtration rate (GFR) is below 50 mL/min/1.73 m² body surface area (BSA) or there is an increased risk of gastrointestinal hemorrhage or there is concomitant use of verapamil. An even more reduced dose of 75 mg twice a day can also be used if two of the above conditions are present in the same patient. Dabigatran is contraindicated if the GFR is <30 mL/min/1.73 m² BSA or there is concomitant use of either phenytoin, carbamazepine, or ketoconazole, amiodarone, verapamil, clarithromycin, rifampicin or antifungal agents, and aminotransferase/aminotransferase is more than twice the normal upper limit.[18]

### Apixaban

Apixaban is a factor Xa inhibitor and has an elimination half-life of about 12 h. Dosage is 5 mg twice a day and 2.5 mg twice a day if the GFR is below 15 mL/min or if 2 out of the following is present in the same patient – age >80 years, weight <60 kg, or GFR <30 mL/min/1.73 m² BSA.[18]

### Rivaroxaban

Rivaroxaban is Xa inhibitor with half-life of about 12 h. Dosage is 20 mg after dinner. Dosage is reduced to 15 mg after dinner if the GFR is below 50 mL/min/1.73 m² BSA but above 30 mL/min/1.73 m² BSA and further reduced to 10 mg after dinner if the GFR is below 30 mL/min/1.73 m² BSA and contraindicated if the GFR is below 15 mL/min/1.73 m² BSA.[18]

### Special scenarios

*Anticoagulation before and after cardioversion (CV) in AF patients.*

CV leads to atrial stunning which results in the decreased mechanical functioning of atria that can last up to 4 weeks resulting in possibility of clot formation. To prevent this NOAC must be started 4 hours before the CV and continue as per $CHA_2DS_2$-VASc score. If the $CHA_2DS_2$-VASc score is >2 continue anticoagulation lifelong. If score is <2 or if AF was present for <48 h before CV, then there is no need to continue OAC beyond 4 weeks after CV.[19,20]

*Coronary artery disease in AF patients*

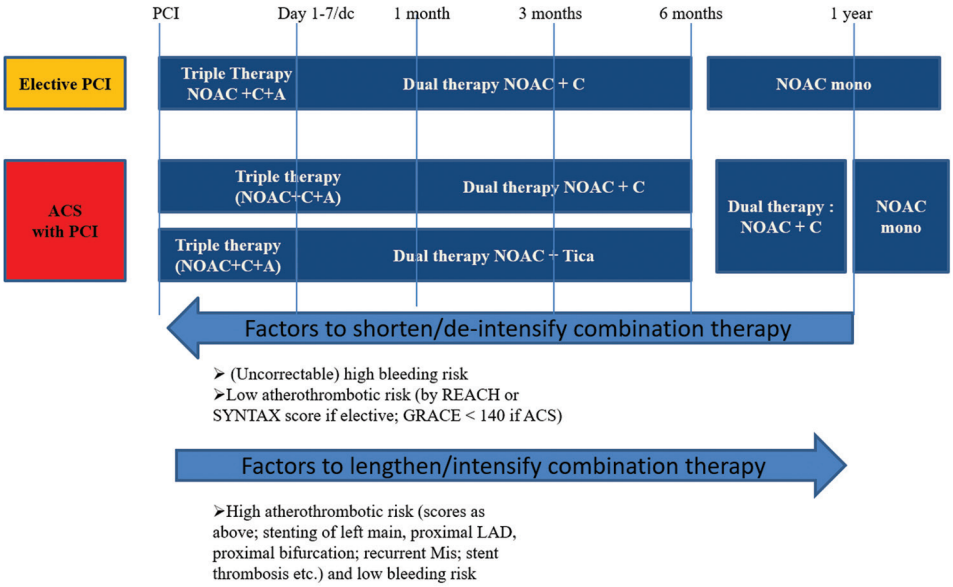
Acute coronary syndrome (acs) with percutaneous coronary intervention (pci) [Table 4]

Patients presenting as ACS with AF dual antiplatelet therapy (DAPT) along with an OAC (preferably a NOAC) are started if there is a moderate to high risk of CVA/STE. Acute anticoagulation can be started with unfractionated heparin (UFH), low molecular heparin (LMWH), or bivalirudin. The triple therapy with a DAPT and NOAC is continued for a period of 1 month if the bleeding risk is low or 7 days if bleeding risk high, then clopidogrel and NOAC are continued until 1 year then clopidogrel is stopped and the NOAC can be continued.[10] AF develops after an ACS and there is an indication for anticoagulation during the 1st year, a NOAC should be started and the need for continuing DAPT should be carefully weighed against the increased bleeding risk. Beyond 1 month after the event, aspirin can be stopped in the majority of such patients.

AF patients undergoing elective PCI [Table 5]

Depending on patient's age, presentation, and left ventricular dysfunction in AF patients only antiplatelet agents are not enough to prevent larger clot formations in the left atrium. To

**Table 4:** Management of AF after PCI




C: Clopidogrel, A: Aspirin

**Table 5:** NOAC and Creatinine clearance

| | Dabigatran | | Apixaban-Edoxaban-Rivaroxaban | |
|---|---|---|---|---|
| No perioperative bridging with LMWH/UFH | | | | |
| Minor risk procedures: – Perform procedure at NOAC trough level (i.e., 12 h/24 h after the last intake). - Resume the same day or latest next day. | | | | |
| | Low risk | High risk | Low risk | High risk |
| CrCl ≥80 mL/min | ≥24 h | ≥48 h | ≥24 h | ≥48 h |
| CrCl 50–79 mL/min | ≥36 h | ≥72 h | | |
| CrCl 30–49 mL/min | ≥48 h | ≥96 h | | |
| CrCl 15–29 mL/min | Not indicated | Not indicated | ≥36 h | |
| CrCl ≤15 mL/min | No official indication for use | | | |

CrCl: Creatinine clearance

balance these effects a dual antiplatelet strategy (with aspirin and clopidogrel), along with a NOAC is started and continued for 7 days when the aspirin is stopped and clopidogrel and NOAC continued for 6 months and then NOAC.[10]

AF with chronic coronary syndrome

The ACC-ECDP Expert Consensus Decision Pathway reported AF in 12% of cases undergoing a PCI.[21] Experts believed following the PCI clopidogrel and a NOAC should be given for a period of 6 months to a year. If the clotting risk is substantial with a usual bleeding risk then aspirin can be added to the above regimen for an initial period of 7–30 days. If the risk of bleeding is high (HAS-BLED equal to or >3), then the NOAC dose needs to be reduced (dabigatran 110 mg twice a or rivaroxaban 15 mg after dinner or apixaban 2.5 mg twice a day). If a patient who is already on a NOAC needs to undergo an elective PCI, then the NOAC must be stopped for 24 h. UFH or LMWH can be used but not fondaparinux. Furthermore, loading with an agent need not be done.[10]

*Ischemic cerebrovascular accident*

Thrombolysis with recombinant tissue plasminogen activator (rtPA) within 4.5 h is contraindicated in patients who are on OAC. rtPA can be given in a patient on VKA if the INR is below 1.7 but not in patients who have taken a NOAC within the past 48 h.[22]

If the patient is on dabigatran or rivaroxaban and thrombolysis is urgently required, then it can be given in case of dabigatran if the aPTT is normal or in case of rivaroxaban after checking dilute PT.

If a patient of ischemic CVA has AF, then OAC can be started immediately if there is no hemorrhagic CVA or large infarct and the blood pressure is below 160/100 mmHg.

The risk of recurrent CVA in patients of CVA/TIA is about 8% in 2 weeks. The risk of hemorrhagic transformation is increased in case of a large infarct, history of any previous hemorrhagic CVA, low platelet counts, microbleeds seen on imaging, older age, or if the patient is on anti-platelet treatment. Without these risk factors, the risk of hemorrhagic transformation is only 1.5% in 14 days.[22]

In case of high risk of hemorrhagic transformation, imaging is repeated after 3 days and OAC started based on the NIHSS CVA severity (National Institute of Health Stroke Scale) – if the NIHSS score is <8, then OAC can be started in 3 days (after the repeat imaging), if the NIHSS is>8 but >16, then OAC can be started in 6 days, if NIHSS is >16 then OAC can be started after 12–14.[23]

*Intracranial hemorrhage*

In a patient who was not on an OAC before ICH, an OAC can be started 4–8 weeks depending on the size of the intracranial bleed[22] and if high bleeding risk, then consider LAAO.

If ICH occurs in a patient on OAC, then the OAC must be stopped. If the patient is more than 70 years old or has a blood pressure of more than BP 200/100 or the bleeding is large, then the OAC can be started after 10 weeks.

*AF in patients with low platelet counts*

Patients with low platelet count have an increased incidence of bleeding when OACS are used. It is recommended that the usual doses of OAC be used if the platelet count is above 50,000/ul with platelet monitoring. If the platelet count is <50,000/uL but more than 30,000/ul, then OAC at half the recommended dose can be used with caution. If the platelet count is below 30,000/uL, then OAC should not be used.[24]

*AF in pregnancy and lactation*

Rivaroxaban, Dabigatran, and Edoxaban are category C as per US FDA (which states-animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks). The Royal College of Obstetricians and Gynecologist's recent guidelines in April 2015 states Non-vitamin K anticoagulants should be avoided in pregnancy, and use of NOACs is not recommended in women who are breastfeeding.[25]

*How to stop and restart a NOAC before surgery*

Often a patient on a NOAC needs to undergo surgery. In such a situation, dabigatran needs to be stopped a day before surgery when the GFR is estimated to be more than 80 mL/min/1.73 m² BSA. These can be restarted on the same day of surgery provided there is no active bleeding or any immediate risk of bleeding. This duration of stoppage is increased to 2 days if the GFR is below 80 but above 50 mL/min/1.73 m² BSA and for 3 days if GFR is below 50mL/min/1.73 m² BSA. This further needs to be increased by one day if the HAS-BLED score is equal to or above 3 and undergoing high-risk surgery. Apixaban and rivaroxaban need to be stopped for 1 day before low-risk and 2 days before high-risk surgery. In case of surgery that involves minor or no bleeding, NOACs need not be stopped.[10]

*How to changeover from one anticoagulant to another?*

Sometimes, a changeover is required from one anticoagulant to another. If a switch is to be made from a VKA to a NOAC then the VKA is to be stopped and the NOAC is started only when the INR falls below 3.0. When there is a need to switch from unfractionated heparin to a NOAC then the UFH infusion can be stopped and NOAC started immediately. When the switch must be made from an LMWH to a NOAC then the LMWH has to be stopped and NOAC started at the time when the next dose of LMWH was initially scheduled.[10]

*How to manage a hemorrhagic complication in patients on NOAC*

Rarely NOACs cause a significant bleed If the NOAC was last taken more than 24 h earlier, then only general treatment is required. This involves giving IV fluids to promote urinary clearance of the NOAC, blood transfusion as required, and using prothrombin complex concentrates as required (not Fresh Frozen Plasma). If this does not stop the bleeding then factor eight inhibitor bypassing activity is required which contains coagulation factors II, IX, X, and Vlla. In such cases, no specific reversal agent is required. If surgery is required and can be postponed by 12 h or more, it should be postponed.

If the bleeding is life-threatening or the surgery required is urgent and cannot be postponed by 12 h, then other than the general measures mentioned above specific reversal agent is required.

- For dabigatran, the reversal agent is idarucizumab which is given as 2 IV boluses of 2.5 mg each separated by 20 min, each bolus given over 15 minutes. This usually reverses the effect of dabigatran within 4 h as seen in the REVERSAL-AD trial of 90 patients.[26]
- For rivaroxaban, the reversal agent is andexanet alfa, which is given as a bolus of 800 mg at a rate of 30 mg/min, then continued as an infusion of 8 mg/min for 120 min.[27]
- For apixaban, the agent is also andexanet alfa but given at half the dosage as for rivaroxaban, both as bolus and infusion.[27]
- A new agent has now been developed called ciraparantag, which can be used as a reversal agent for all NOACS (DTIs as well as Factor Xa inhibitors).

## CONCLUSION

AF is a common rhythm disorder that makes the patient prone to develop CVA/STE which increases ACM and worsens the quality of life. Before starting NOAC a detailed knowledge about the risk and benefits and dept of the patient's comorbidity and personal preference should be known. For patients currently on warfarin and desiring conversion to one of the newer agents, NOACs would be recommended only for patients who have proven excellent medication compliance in the past. For patients already on these agents, close clinical follow-up for adverse events must be pursued. NOAC are new clinical alternatives to warfarin for NVAF.

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