

 <p>ISSN NO. 2320-5407</p>	<p>Journal Homepage: - <a href="http://www.journalijar.com">www.journalijar.com</a></p> <p><b>INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)</b></p> <p>Article DOI: 10.21474/IJAR01/12525 DOI URL: <a href="http://dx.doi.org/10.21474/IJAR01/12525">http://dx.doi.org/10.21474/IJAR01/12525</a></p>	 <p>INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR) ISSN 2320-5407 Journal Homepage: <a href="http://www.journalijar.com">http://www.journalijar.com</a> Article DOI: 10.21474/IJAR01/12525</p>
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### RESEARCH ARTICLE

## ROLE OF NOVEL ORAL ANTICOAGULANTS (NOACS) IN PATIENTS WITH ATRIAL FIBRILLATION CARDIOVERSION- AN EXECUTIVE SUMMARY

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### Manuscript Info

#### Manuscript History

Received: 23 December 2020

Final Accepted: 25 January 2021

Published: February 2021

#### Key words:-

Atrial Fibrillation, Cardioversion, Rivaroxaban, Warfarin, NOAC, Stroke, Systemic Embolism, Diabetes Mellitus, Coronary Artery Disease

### Abstract

In patients with non-valvular atrial fibrillation (NVAF), oral anticoagulation is necessary for prevention of stroke and systemic embolism especially during cardioversion. While Vitamin K antagonists (VKAs) have historically been the standard of care, these medications are limited by numerous food and drug interactions with requirements for frequent monitoring (INR) and dose adjustments. Over the past decade, several novel oral anticoagulants (NOACs) have been developed to directly inhibit factor IIa/thrombin (dabigatran) or activated factor X (apixaban, rivaroxaban, edoxaban). These medications have been shown to be at least as effective as warfarin for stroke prevention in NVAF with more favorable safety profiles. However, their advantages are underscored by a lack of specific antidotes and assays quantifying their anticoagulant effects. This review addresses how well do the Rivaroxaban prevents stroke and systemic embolism compare to VKAs in patients with NVAF, with a special focus on high-risk populations, including the elderly, those with renal disease, diabetes mellitus, coronary artery disease, and previous stroke.



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### Introduction:-

Atrial fibrillation (AF) Is a type of a cardiac arrhythmia characterized by disorganized electrical activity in the atria with a completely irregular ventricular response [1]. Palpitation, fainting, syncope, dyspnea or chest pain are common symptoms [2]. Hypertension and valvular heart disease are the 2 most common risk factor for AF [3,4]. According to ACC/AHA/ESC guideline AF was classified as 4 categories: 1 first detected episode, 2 paroxysmal (spontaneous terminate <7days and sometimes <48h), 3 persistent (not self-terminating, lasting >7days or prior cardioversion), 4 permanent (not terminated, or terminated but relapsed, no cardioversion attempt). Atrial fibrillation causes blood flow in left atrium to become stasis increases the risk of thromboembolic events as a result of clot formation. Recently, AF is considered a major risk factor for stroke, independently increasing the risk about 5 folds across all age group [5]. In addition, AF is associated with severe complication and increased mortality and morbidity [6,7]. Rate and rhythm controls are gold standard management for AF patients. However, restoration of sinus rhythm without coagulation control is associated with increased risk of stroke rate by 5-7% [8,9]. Transesophageal echocardiography (TEE) can be performed to exclude the majority of left atrial (LA) thrombi ("early strategy"). It appears clear that in patients scheduled for cardioversion it is necessary to follow a strict anticoagulation protocol that should be started at least 3 weeks before and continued for 4 weeks after if AF is for longer than 48 h or has unknown onset ("standard strategy") [10]. Rivaroxaban is one among other Non-vitamin K antagonist oral anticoagulants (NOACs) and its effects are at least non-inferior to Vitamin K Antagonists (VKAs) for stroke and systemic embolism prevention in patients with non-valvular atrial fibrillation (AF). We aimed to

evaluate the efficacy and safety of NOACs in patients undergoing cardioversion through a systematic review and meta-analysis. In addition, currently, an increasing number of patients with AF are treated with Rivaroxaban instead of vitamin k antagonists, because due to the lower risk of intracranial bleeding and hemorrhagic stroke as well due to absence of a need for routine INR monitoring [11], Other advantageous aspects of Rivaroxaban are the rapid onset of action (2–4 h), shorter half-life and fewer interactions with food and drugs [12].

European Heart Rhythm Association proposal for a universal new oral anticoagulation card. A patient information card is crucial, both for the patient (instructions on correct intake; contact information in case of questions) as for health care workers (other care-takers are involved; renal function; follow-up schedule; concomitant medication, etc.). We present a generic and universal card that could serve all patients under new oral anticoagulant therapy.

<h2 style="text-align: center;">Atrial fibrillation</h2> <h3 style="text-align: center;">oral anticoagulation card</h3> <p style="text-align: center;">for non-vitamin-K anticoagulants</p>	
Patient name:	DOB:
Patient address:	
Oral anticoagulant, dosing, timing, with or without food:	
Treatment indication:	
Treatment started:	
Name and address of anticoagulant prescriber:	
Telephone number of prescriber or clinic:	
 <p><b>EUROPEAN Heart Rhythm Association</b> <small>EUROPEAN SOCIETY OF CARDIOLOGY</small></p>	 <p><b>EUROPEAN SOCIETY OF CARDIOLOGY</b></p>
<p>More info:</p> <p><a href="http://www.NOACforAF.eu">www.NOACforAF.eu</a></p> <p><a href="http://www.noacforaf.eu">www.noacforaf.eu</a></p>	

[illegible][illegible]

## Important patient instructions

**Take your drug exactly as prescribed (once or twice daily).  
No drug is no protection!**

**Never stop your medicine without consulting your physician.**

**Never add any other medication without consulting your physician,  
not even short-term painkillers that you can get without prescription.**

**Alert your dentist, surgeon or other physician before an intervention.**

## Concomitant medication

Name:	Dose:

## Emergency information

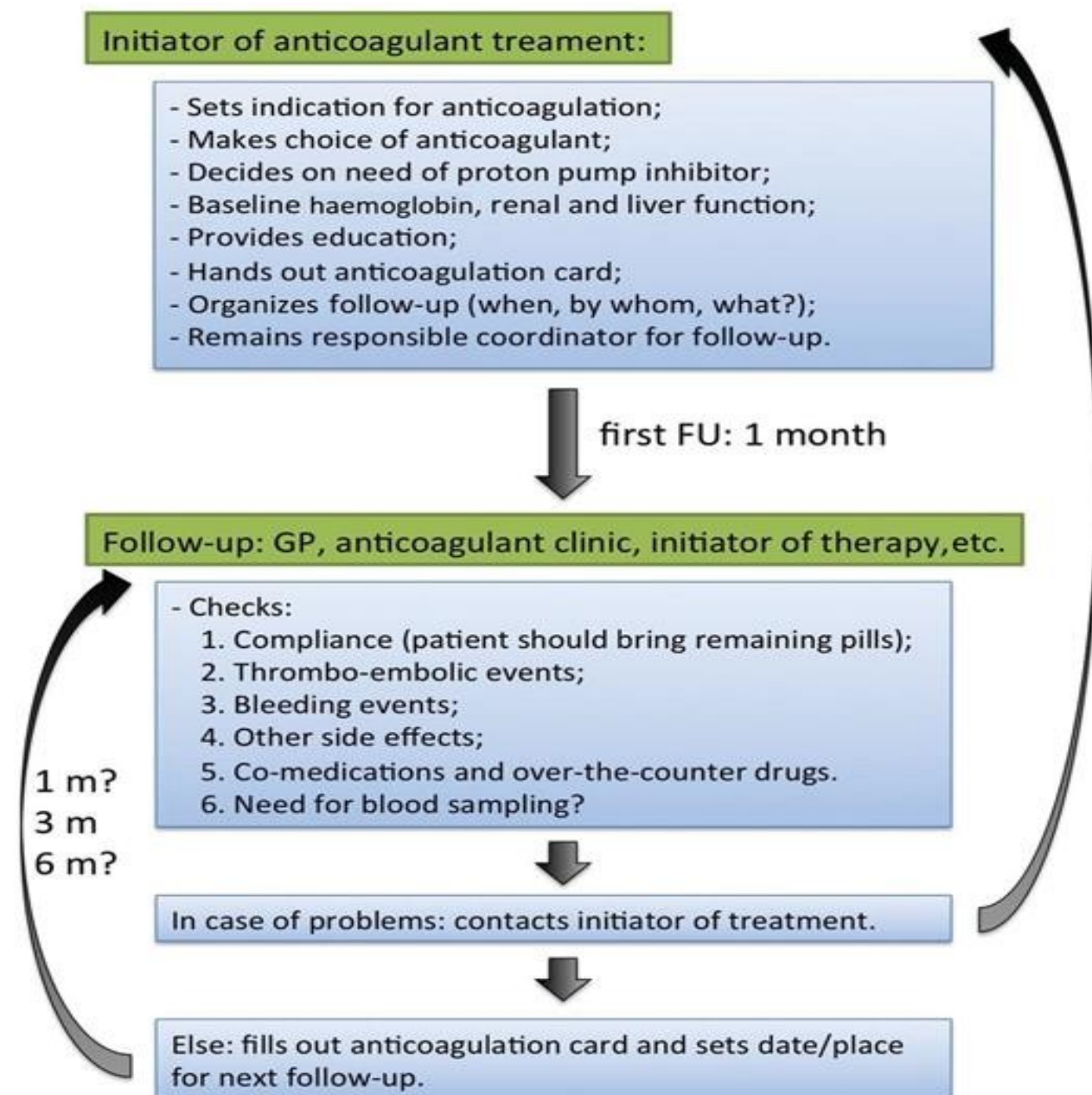
Standard tests do not quantitatively reflect level of anticoagulation!

**Name & telephone of patient relative to contact if emergency:**

**Patient blood group (+ physician signature):**

### General discussion:-

Structured follow-up of patients on new oral anticoagulants. Structured follow-up of patients on new oral anticoagulants is mandatory to ensure safe and effective drug intake. The anticoagulation card, as proposed in *Figure 1*, is intended to document each planned visit, each relevant observation or examination, and any medication change, so that every person following up the patient is well-informed. Moreover, written communication between the different (para)medical players is required to inform them about the follow-up plan and execution.



### Cardioversion in AF:-

Restoration of sinus rhythm with cardioversion is an important treatment option in AF and has a high success rate when arrhythmias are detected early. However, in atrial fibrillation patients, blood clots can form in left atrium. Cardioversion with a blood clot present in left atrium may knock loose a blood clot. If the clot (embolus) travels to your brain, it can cause a systemic embolism especially stroke. To avoid this, patients with AF of >48 hours in

duration and those in whom the time of onset is unknown for a period of at least 3 weeks before and 4 weeks after cardioversion [22,23]. transesophageal echocardiography (TEE) is often used to check for the presence of blood clots before cardioversion.

#### **Clinical pharmacology of Rivaroxaban:**

Rivaroxaban is an oral direct factor Xa inhibitor that is used in the prevention and treatment of thromboembolic disorders during the advanced development of thrombi. Rivaroxaban exhibits predictable, dose-proportional pharmacokinetics (PK), with high oral bioavailability and a rapid onset of action - the maximum effect of rivaroxaban is observed to occur 2 hours after its administration (11).

Rivaroxaban (10 mg tablets) are well absorbed (80% bioavailability) with no effect of food on absorption or pharmacokinetic parameters with Plasma concentrations peak at 2.5–4 h [14,15]. The plasma elimination half-life is 5–9 h in young adults and 11–13 hours in older people due to the age-related decline in renal function. This permits once- or twice-daily dosing.

Rivaroxaban is metabolized by liver enzymes (principally cytochrome P450 3A4), and also by cytochrome-independent mechanisms. There are no known active metabolites. Rivaroxaban has a dual mechanism of excretion. Approximately 66% of the dose is excreted via the kidneys, in roughly equal proportions of rivaroxaban and inactive metabolites. The remainder is excreted by the fecal-biliary route. Intestinal excretion of rivaroxaban appears to be mediated, at least in part, by P-glycoprotein, a transport protein, because potent P-glycoprotein inhibitors will increase plasma concentrations of rivaroxaban.

#### **Anticoagulant regimens- Switching between these:**

It is essential to protect the continuation of anticoagulant treatment while limiting the danger for draining when exchanging between various anticoagulant treatments. This requires bits of knowledge into the pharmacokinetics and pharmacodynamics of various anticoagulation regimens, deciphered with regards to the individual patient. Functional exchanging situations have been portrayed in the full record, for VKA or a parenteral anticoagulant to NOAC and the other way around. Particularly for the conditions where NOAC treatment ought to be changed to VKA, alert is needed: because of the moderate beginning of activity of VKAs, it might require 5–10 days before an INR in remedial reach is acquired, with enormous individual varieties. Consequently, the NOAC and the VKA ought to be directed associatively until the INR is in a reach that is viewed as proper.

Since NOACs may additionally affect the INR (particularly the FXa inhibitors), impacting the estimation while on consolidated treatment during the cover stage, it is significant (I) that the INR be estimated not long before the following admission of the NOAC during associative organization, and (ii) be re-tried 24 h after the last portion of the NOAC (for example sole VKA treatment) to guarantee satisfactory anticoagulation. It is likewise prescribed to intently screen INR inside the main month until stable qualities have been achieved (for example three successive estimations ought to have yielded values somewhere in the range of 2.0 and 3.0).

#### **Rivaroxaban and Vitamin K Antagonists:**

Truly, Vitamin K opponents (VKAs) were the solitary class of oral anticoagulants accessible to forestall thromboembolism. While VKAs have been appeared to lessen stroke by up to 60%, their utilization is restricted by a thin remedial list, different food and medication communications, and necessities for regular portion changes [16]. These restrictions have meant variable patient adherence and a general underutilization for stroke counteraction [17,18]. The epic oral anticoagulants (NOACs) apixaban, rivaroxaban, dabigatran, and edoxaban were in this manner planned in order to address the difficulties of keeping up restorative anticoagulation across a wide scope of AF patients.

These meds work by portion subordinate hindrance of thrombin(dabigatran) or initiated factor X (rivaroxaban, apixaban, edoxaban). Contrasted with customary VKAs, NOACs offer advantageous fixed dosing, quick beginning of activity, and no requirement for routine observing INR [19]. Every one of these meds were exclusively approved in huge stage III clinical preliminaries to be in any event as successful and protected as warfarin for forestalling stroke and foundational embolism (SE) in patients with non-valvular atrial fibrillation (NVAf) [20,21]. For the motivations behind this paper, we will audit the writing for the 4 milestone NOAC preliminaries and their suggestions for different high-hazard quiet populaces.



**Role of Rivaroxaban:**

Non-valvular AF is an irregular heart rhythm in the Atrium that is not caused by heart's valves. Many Conditions that may specifically increase the risk of developing nonvalvular AF include: Pulmonary disease, obesity, diabetes, obstructive sleep apnea, alcoholism, hyperthyroidism, metabolic syndrome.

AF can cause a number of problems, including blood pooling in parts of the heart. The consequence of this pooling can mean that less blood is available to be pumped to the rest of the body. If a blood clot forms in the pooled blood, it could reach the brain and cause a stroke.

Treatment will vary according to symptoms, how severe the symptoms are, and whether a person already has heart disease. If there are no symptoms or related heart problems, the heart may return to a normal rhythm without treatment. The main goals of treatment are (American heart association):

1. Restoring the heart to a normal rhythm (called rhythm control)
2. Reducing an overly high heart rate (called rate control)
3. Preventing blood clots (called prevention of thromboembolism such as stroke)
4. Managing risk factors for stroke
5. Preventing additional heart rhythm problems
6. Preventing heart failure

Guidelines (ESC) for the management of AF at the approved doses of 20 mg once daily for patients with CrCl >50 and 15 mg once daily for patients with CrCl 15–49 mL/min [33,34]. Clinical experience with rivaroxaban is increasing rapidly. Rivaroxaban has the broadest range of indications of all the NOACs, supporting efficacy and safety across a wide spectrum of patients.

Rivaroxaban (NOACs) for stroke prevention in AF is useful, because it appears safer than vitamin K antagonists (VKA), especially with respect to intracranial hemorrhage [25].

New meta-analysis summarizes the best available evidence on Rivaroxaban for cardioversion of AF. The principal findings of Rivaroxaban is recommended in the current version of the European Society of Cardiology's study are the following: (1) NOACs were as safe as VKA in the prevention of stroke or systemic embolism in patients undergoing cardioversion; (2) The rate of primary events was very low in the four studies and in both therapeutic arms (19 events in 3,500 patients). The confidence intervals of estimates were still wide and pooled data were not powered enough to establish non-inferiority of NOACs). The rates of other clinically significant outcomes such as major bleeding, myocardial infarction, and mortality did not differ significantly among interventions [23]. More than 90% of thrombi in patients with NVAF originate in the left atrial appendage (LAA) [26]. The incidence of LA/LAA thrombus under treatment with VKAs ranges between 0.6% and 7% and LAA thrombi seems to persist in up to 40% of patients under VKA treatment with a poor prognosis[27,28] To date, several studies have been performed in order to estimate the incidence of thrombi in AF patients treated with one or other therapeutic strategies.

In a retrospective study, Wyrembak et al estimated that the incidence of LAA thrombus was higher on TEEs performed in patients treated with warfarin (1.55%, 8 of 517) than in those treated with Rivaroxaban (0.24%, 1 of 420,  $p=0.047$ ) within 937 routine pre-AF ablation TEE procedures performed in patients treated for at least 4 consecutive weeks before the TEE with warfarin (N=517) or NOAC (N=420; N=203 rivaroxaban, N=90 apixaban, N=127 dabigatran)[29]. These results were also confirmed by Zylla et al who demonstrated that the prevalence of intracardiac thrombi undergoing therapy with phenprocoumon was significantly higher (17.8%) than in the rivaroxaban group (4.1%) or dabigatran (3.8%) in a high-risk population (median CHA2DS2-VASc score of 4) [30].

Gawalko and coworkers performed a single-center observational study of 1,033 consecutive patients with AF who underwent scheduled TEE before catheter ablation or cardioversion for AF in anticoagulation therapy with VKAs (50.9%); rivaroxaban (26.8%), dabigatran (22.2%) and apixaban (0.1%). A total of 174 patients were excluded because they were without any prior oral anticoagulation or underwent bridging with heparin before TEE or they had discontinued NOACs (Rivaroxaban) in the previous 3 weeks. There were no differences in baseline characteristics (including the CHA2DS2-VASc and HAS-BLED scores) as well as in the incidence of LAA thrombus (VKAs, 6.9%; NOACs, 5.5%;  $p=0.40$ ) and dense spontaneous echo contrast (VKAs, 5.3%; NOACs, 3.3%;  $p=0.18$ ) between patients on VKAs and those on NOACs. Compared with patients treated with dabigatran, the

frequency of LAA thrombus in both NOAC groups was comparable (6.8% in the dabigatran group vs 4.4% in the rivaroxaban group;  $p=0.29$ ), while dense spontaneous echo contrast occurred more often in dabigatran-treated patients (5.2% vs 1.7%;  $p=0.06$ ) [31]. The low incidence of thrombi has also been confirmed in a real-life study including AF patients ( $N=414$ ) who underwent catheter ablation of AF ( $N=220$ , 53.1%) or scheduled ECV ( $N=194$ , 46.9%) and treated with NOACs.68 The incidence of LAA/LA thrombi seems to be low (3.6%), regardless of the type of NOAC, depending mostly by CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores (in particular, history of heart failure, diabetes and previous stroke/TIA), corroborating findings from other studies [31,32]

#### **Complications of Rivaroxaban:**

The most common types of rivaroxaban-related major bleeding are gastrointestinal tract and intracranial hemorrhages. [8] Rivaroxaban is not recommended for use in patients with renal insufficiency (estimated glomerular filtration rate  $<30$  mL/minute). In addition, it is recommended that kidney functions be assessed at regular intervals in patients using the drug.

One case report had been studied by (Salih Kılıç, M.D, Saraçoğlu, M.D, Gülin Alkan, M.D) in an 89-year-old woman with a history of diabetes, hypertension, heart failure, and atrial fibrillation with Rivaroxaban treatment at 20 mg/day had been initiated 6 months and the patient did have a history of very frequent use of non-steroidal anti-inflammatory drugs (NSAIDs) recently. She developed acute renal failure, and was considered to have rivaroxaban-induced Alveolar hemorrhage (AH) [36].

Rivaroxaban (the first direct factor-Xa inhibitor), has been approved for stroke prophylaxis in patients with non-valvular AF, as well as for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery and for the treatment of deep vein thrombosis. There is no requirement for coagulation monitoring with rivaroxaban in routine clinical practice. However, in certain clinical circumstances such as life-threatening bleeding or an emergency operation the measurement of the thromboplastin time with a sensitive reagent will deliver first information. A quantitative determination of rivaroxaban plasma concentration is possible using an anti-factor Xa assay. In the case of a patient under long-term anticoagulation with rivaroxaban requiring an elective surgery, a discontinuation of rivaroxaban 20 to 30 hours before the operation is sufficient to normalize the associated bleeding risk, as long as the renal and liver function is normal.

Many individual comorbid medical conditions have been associated with elevated risks for bleeding in anticoagulant treatment. These include a history of congestive heart failure, cerebrovascular disease, hepatic or renal disease, diabetes mellitus, history of bleeding (especially in the gastrointestinal tract), and anemia. [36,37]. However, new oral anticoagulants have generally been associated with lower rates of fatal bleeding, individual comorbid medical conditions associated with elevated risks for bleeding should be considered before starting a new oral anticoagulant. [36,38] In addition, there are several bleeding risk scores to estimate the risk of bleeding in anticoagulated patients. Bleeding risk assessment can be performed using the well-validated HAS-BLED [hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (65 years), drugs/alcohol concomitantly] score. A high bleeding risk score should generally not result in withholding the anticoagulant.[36] Rather, bleeding risk factors and treatable factors (i.e., hypertension, NSAID use, anemia, impaired renal or liver function) should be identified. Accurate assessment of renal function is a prerequisite for the correct management of people at risk of developing chronic kidney disease. Serum creatine, the most widely used surrogate marker of glomerular filtration rate, is inaccurate with increasing age, particularly in sick and/or malnourished elderly people. [38] Current guidelines recommend that the 2 most commonly used equations to estimate glomerular filtration rate - the Modification of Diet in Renal Disease Study method and the Cockcroft-Gault formula - be used to estimate glomerular filtration rate in the clinical setting.[38]It is of vital importance that patients taking new oral anticoagulants are monitored at certain intervals for renal and liver function, and are informed about drugs that affect renal functions.

#### **Ensuring compliance with new oral anticoagulant intake:**

The anticoagulant impact of NOACs blurs quickly 12–24 h after the last admission. In this way, exacting treatment consistence by the patient is urgent for sufficient security. Doctors ought to create approaches to enhance consistence, which is known to be  $\leq 80\%$  for most medications in every day practice. There is no logical information yet on the genuine consistence of NOACs in non-preliminary conditions, nor on how it can best be improved. By the by, all way to streamline consistence ought to be thought of. These include: contemplations on picking a NOAC with once every day or twice day by day consumption; rehashed tolerant training, too of their relatives; an

unmistakably pre-determined subsequent timetable between broad professional, cardiologist, or electrophysiologist (see 'Commonsense beginning up and follow-up plan for patients on new oral anticoagulants'); potentially innovative guides like medicine boxes or cell phone applications if their viability could be demonstrated; organized drug store information base (as accessible in certain nations). At long last, in NOAC patients in whom low consistence is suspected in spite of appropriate training and extra devices, change to VKAs could be thought of. Additionally, a few patients may themselves lean toward INR observing to no checking.

#### **How to manage if there happens dosing errors:**

Questions identifying with dosing blunders are normal in day by day practice. Regularly, the patient calls the emergency clinic, office or even a public toxic substance community. It is fitting to give staff laborers of these call fixates with clear guidelines on the best way to prompt patients in these conditions. To forestall circumstances as portrayed underneath, patients on NOACs ought to be encouraged to utilize very much named week by week pill holders, with isolated spaces for each portion. In the event of a missed portion, no twofold portion ought to be taken to compensate for missed individual dosages. The failed to remember portion may, nonetheless, be taken until midway the dosing span (for example up to 12 h for a once every day dosing). On the off chance that that is absurd any longer, the portion ought to be skipped and the following booked portion ought to be taken. On the off chance that a twofold portion has erroneously been taken, one could pick to swear off the following arranged portion. At times, the patient isn't certain about if a portion has been taken. For NOACs with a BID dosing routine, one could encourage to not take another pill, however to simply proceed with the arranged portion routine, for example beginning with the following portion at the 12 h span. For NOACs with a QD dosing routine, one could encourage to take another pill and afterward proceed with the arranged portion routine. In the event of excess, contingent upon the measure of suspected excess, hospitalization for observing or critical measures ought to be prompted (see likewise 'What to do if there is a (suspected) glut without dying, or a thickening test is showing a danger of bleeding?').

#### **Limitations:-**

##### **Patients undergoing an urgent surgical intervention:**

On the off chance that a crisis intercession is required, the NOAC ought to be stopped. Medical procedure or intercession ought to be conceded, if conceivable, until in any event 12 h and in a perfect world 24 h after the last portion. Assessment of normal coagulation tests (aPTT for DTI; touchy PT for FXa inhibitors) or of explicit coagulation test (dTT for DTI; chromogenic examines for FXa inhibitors) can be thought of if there is worry about the pharmacokinetic fading of the anticoagulant impact (for example renal deficiency or potentially attending conditions). By and by, such methodology has never been assessed, and hence can't be suggested and ought not be utilized regularly.

##### **New oral anticoagulants vs. vitamin K antagonists in atrial fibrillation patients with a malignancy:**

Patients with malignancies are at an expanded danger for thrombo-embolic occasions. Numerous types of malignancy connect straightforwardly or in a roundabout way with the coagulation framework. Also, disease treatment may prompt seeping through neighborhood wounds (medical procedure), tissue harm (illumination), or fundamental antiproliferative impacts which will diminish platelet check and capacity (chemotherapy, a few types of irradiation).<sup>38</sup> There is almost no controlled information for antithrombotic treatment in AF patients with danger. Dynamic harm for the most part was a prohibition measure in NOAC preliminaries. Antithrombotic treatment in patients with AF and enduring a danger needs conversation among cardiologist and oncologist, thinking about the effect of the disease on dismalness and mortality, the particular oncologic treatment utilized, and the foreseen impacts of tumor and treatment on both thrombo-embolic danger and draining danger. At the point when anticoagulant treatment should be started in a patient with danger, treatment with VKAs or heparins ought to be considered over NOACs, due to the clinical involvement in these substances, the chance of close checking (for VKAs and unfractionated heparin, UFH), and inversion choices (for VKAs and UFH). In AF patients steadily treated with a NOAC, who create malignancies for which they need to get modestly myelosuppressive treatments, continuation of NOACs might be defendable. At the point when a strong myelosuppressive chemotherapy or radiation treatment is arranged, transitory portion decrease or suspension of NOAC treatment ought to be thought of, and additionally explicit observing established, including tedious full-blood checks (counting platelets), standard checking of liver and renal capacity, and cautious clinical assessment for draining signs. Gastric insurance with PPI or H2-blockers isn't contraindicated and ought to try and be considered in all patients treated with anticoagulants.

However, these studies still have some limitations such as small number of participants, loss of follow up and difference in in CHA2DS2-VASc risk scores.

### Conclusion:-

The strong scientific evidence available demonstrates that rivaroxaban (NOACs) are preferable to VKA in patients with NAVF (this position is supported by the most recent European and American guidelines, meta-analyses retrospective studies and in particular in CHA2DS2-VASc risk scores  $\geq 1$  patients scheduled for cardioversion it is reasonable to prefer rivaroxaban instead of VKA anticoagulation therapy.

However, there are also some gaps for the review. Further doing researches are necessary to get more detail information. I aim to do research more about some areas such as: difference of effects between kind of novel oral anticoagulants (NOACs) to prevent stroke and systemic embolism in atrial fibrillation cardioversion, effectiveness of rivaroxaban on the mortality rate depend on each CHA2DS2-VASc risk scores in atrial fibrillation patients and risk of bleeding in atrial fibrillation patients with novel oral anticoagulants and vitamin k antagonists.

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