

## Review Article

# Oral anticoagulation therapy: current challenges in Indian scenario

Ajit Menon<sup>1\*</sup>, Joy Thomas<sup>2</sup>, N. R. Ichaporia<sup>3</sup>, Prasant Kumar Sahoo<sup>4</sup>, T. Govindan Unni<sup>5</sup>

<sup>1</sup>Department of Interventional Cardiology, Lilavati Hospital and Research Centre, Mumbai, Maharashtra, India

<sup>2</sup>Department of Cardiology and Electrophysiology, Global Hospital, Chennai, Tamil Nadu, India

<sup>3</sup>Department of Neurology and Stroke, Jehangir Hospital, Pune, Maharashtra, India

<sup>4</sup>Department of Cardiology, Apollo Hospital, Bhubaneswar, Odisha, India

<sup>5</sup>Department of Cardiology, Jubilee Hrudhayalaya, Thrissur, Kerala, India

**Received:** 17 March 2020

**Accepted:** 28 April 2020

### \*Correspondence:

Dr. Ajit Menon,

E-mail: [jaeajit@gmail.com](mailto:jaeajit@gmail.com)

**Copyright:** © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

## ABSTRACT

Over the past decade, the burden of thromboembolic diseases has increased in India; however, there is a huge gap between the diagnosis and treatment of these ailments. This is further complicated by the presence of various options for anticoagulation therapy and the absence of a clinical consensus on the use of these anticoagulants. To address this issue and establish consensus statements on the use of anticoagulation therapy in Indian settings, an expert consensus was developed in alignment with the latest available evidence. A group of 38 clinical experts discussed, in detail, various case-based scenarios on stroke prevention in atrial fibrillation (AF), anticoagulation for patients with valvular heart disease, stroke, or deep-vein thrombosis. Anticoagulation management options for special populations, including patients with renal dysfunction, elderly patients, and pregnant women, were also discussed in detail. The key opinions the experts (cardiologists, cardiovascular and thoracic surgeons, consulting physicians, and neurologists) are intended to address gaps in Indian clinical practice concerning anticoagulation therapy. Based on scientific evidence, clinical experience, and guidelines on the use of anticoagulation therapy, various consensus statements were proposed. This document was drafted, reviewed, validated, and modified by the expert panel until a final agreement was reached. This pioneering consensus document will lay the foundation for future anticoagulation education modules based on evidence-based treatment approaches for Indian clinicians.

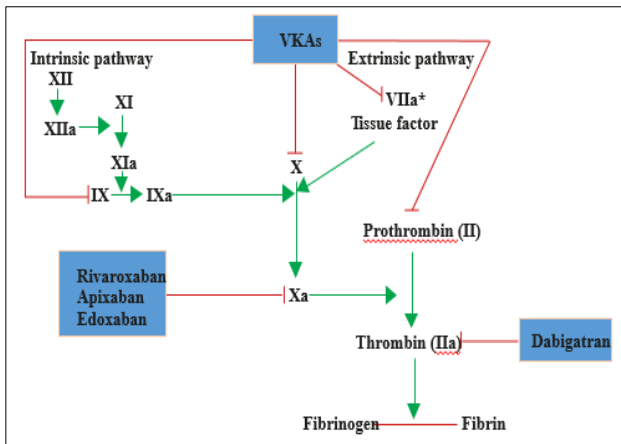
**Keywords:** Atrial fibrillation, Dabigatran, Deep-vein thrombosis, Low molecular weight heparins, Non-vitamin K dependent oral anticoagulants, Vitamin K antagonists

## INTRODUCTION

Globally, thromboembolic disorders such as venous thromboembolism (VTE), and stroke by atrial fibrillation (AF) are major public health concerns whose incidence is on the rise.<sup>1</sup> Anticoagulant therapy is essential for the management and prevention of various thromboembolic diseases.<sup>2,3</sup> Vitamin K antagonists (VKAs), such as warfarin and acenocoumarol, have been the mainstay of anticoagulation therapy and are mostly used for long-term anticoagulant therapy.<sup>4,5</sup>

Low molecular weight heparins (LMWHs) and adjusted-dose warfarin are also routinely used for VTE prophylaxis. Another set of new oral anticoagulant agents, i.e. non-vitamin K dependent oral anticoagulants (NOACs), including agents such as dabigatran, rivaroxaban, and apixaban, have gained increased clinical acceptance in the past decade.<sup>6,7</sup> The mechanism of action of various anticoagulants is shown in Figure 1. Dabigatran has been extensively studied in the context of stroke prevention. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RELY) trial showed that

dabigatran is associated with a lower risk of major bleeding, ischemic stroke, intracranial bleeding, and mortality compared to VKAs.<sup>8</sup>



**Figure 1: Mechanism of action of various anticoagulants.<sup>6</sup>**

Vitamin K antagonists and NOACs act by targeting various factors in the coagulation cascade. VKAs act on various nonactivated factors, while NOACs inhibit specific, activated factors. NOACs do not require antithrombin to exert their effects.<sup>6</sup>

A few limitations of VKAs, such as the narrow therapeutic window, frequent dose adjustments, and numerous drug-drug and drug-food interactions, make it necessary for periodic monitoring of patients. The key features of VKAs are depicted in Box 1. With advantages such as the requirement of less frequent monitoring and a relatively low risk of intracranial or intracerebral bleeding, NOACs have a better safety profile.<sup>9</sup>

Box 1- Features of VKAs.<sup>9</sup>

- Extensively used in clinical practice
- Act by reducing the concentration of four coagulation factors; hence their effects can be easily reversed
- Relatively safe for use in patients with impaired kidney function
- Cost-effective

In the Indian scenario, VKAs are the most prescribed anticoagulants due to comfort level developed over the years by the clinicians. However, there are a few issues specific to the use of VKAs in India, including: difference in dietary patterns in the region compared to the western world; use of nonsteroidal anti-inflammatory drugs (NSAIDs) and over-the-counter drugs; lack of a widespread network of laboratories providing standardized measurement of prothrombin time (PT)/international normalized ratio (INR) monitoring; scarce efficacy and safety data on new anticoagulant

agents; and lack of region-specific anticoagulation guideline/recommendations.<sup>10</sup>

Although international evidence-based guidelines do exist, they do not cater to the situational and specific needs of the Indian region. Moreover, there is an urgent need for enhancing the knowledge of Indian clinicians regarding the use of newer anticoagulants in varied populations.

Hence, to collate region-specific clinical judgments and develop an educational module on anticoagulation for Indian practicing clinicians, a national meeting was held in Mumbai, India in January 2018. A total of 38 clinical experts (cardiologists, cardiovascular and thoracic surgeons, consulting physicians, and neurologists) across India discussed existing global guidelines, current evidence on anticoagulation management, and various case-based scenarios.

This document summarizes the key collective clinical judgments of the panelists. However, the final decision regarding treatment must be individualized. Key expert opinions on the discussed topics are discussed under various headings.

## REVIEW OF LITERATURE

### *Anticoagulation management in different patient populations*

Atrial fibrillation is a common arrhythmia. Non-valvular AF (NVAf) and valvular AF are reliable predictors of stroke, and the use of oral anticoagulant agents constitutes the primary strategy to prevent stroke in patients with valvular and NVAf.<sup>11</sup>

Anticoagulation is an essential part of therapy in patients with valvular heart disease (VHD) to reduce stroke and systemic embolism. Valvular heart disease is associated with a 1.8 to 3.4-fold higher risk of AF in men and women, respectively.<sup>12</sup> The risk of stroke is increased fourfold in patients with NVAf and 17-fold in patients with VAF.<sup>12</sup> Effective antithrombotic therapy, primarily with VKAs and with the INR in the target range, is crucial in patients with mechanical heart valves and prosthetic heart valves.<sup>12</sup> Periodic INR determination through dedicated anticoagulation clinics is associated with lower rates of complications compared with standard care.<sup>12</sup>

In the case of pregnant women with pre-existing heart disease, anticoagulation therapy should be carefully selected to avoid any complications during pregnancy.<sup>1</sup> Additionally, pregnancy is a prothrombotic state and hypercoagulability leads to close to a fivefold increase in the risk of VTE during pregnancy. Hence, the main aim of therapy should be to attenuate the risk of maternal hemorrhagic and developmental anomaly in the growing fetus.<sup>13,14</sup>

### ***Disease burden of stroke and VTE: evidence from clinical studies***

There has been a significant increase in the global stroke burden over the past two and a half decades.<sup>15</sup> According to the 2013 Global Burden of Disease (GDB) study, stroke is the second-leading global cause of death, accounting for approximately 11.8% of all deaths worldwide.<sup>15</sup> It is the third-most common cause of disability, accounting for about 4.5% of disability-adjusted life-years (DALYs) from all causes.<sup>15</sup>

In developing countries such as India, the burden of stroke is enormous. The incidence rate of stroke in India is 119-145/100,000 population. The prevalence and incidence rates are higher in women compared to men.<sup>16</sup> A multicenter real-world registry by Kamekar et al, reviewing 949 medical records from three sites in India reported acute DVT without pulmonary embolism (PE), acute DVT with PE, and PE alone in 64% (352/549), 23% (124/549), and 13% (73/549) of patients, respectively. The annual incidence of acute DVT (with or without PE) increased from 2006 to 2010 at all three sites.<sup>17</sup> A clinical trial in patients with acute VTE revealed that dabigatran was noninferior to warfarin for the prevention of recurrent or fatal VTE despite having a lower risk of bleeding in patients receiving dabigatran.<sup>18</sup>

## **DISCUSSION**

### ***Stroke prevention in a patient with non-valvular AF***

The VKAs are the preferred choice of anticoagulant in patients with mechanical heart valves or severe mitral stenosis. Patients who do not have mechanical heart valves or severe mitral stenosis, stroke risk stratification is done by CHA2DS2-VASc score, and the oral anticoagulants (OACs) are considered based on the resultant score. Since OACs help in preventing ischemic stroke in patients with AF, they should be used in all patients with AF, except in patients at a very low stroke risk.<sup>19</sup>

#### *Key expert opinions*

- Most of the experts recommended NOACs over VKAs in the management of NVAf. With regards to dabigatran, if the patient has a CHADS2-VASc score of 3, nearly half of the clinical experts favored to go with the guideline-recommended dose of dabigatran. However, the experts strongly opined that 110-mg twice-daily dose should be considered as it is associated with a lower incidence of hemorrhagic events than the recommended 150-mg dose. Dabigatran 150 mg can be considered in younger patients, particularly when creatine clearance values are normal.
- Majority of the experts recommended dabigatran for long term/lifelong in AF patient with stable coronary artery disease and follow-up period as 3 to 6 months despite the European heart rhythm association

(EHRA) guidelines recommending blood sampling and follow-up visit in AF patients to be once in a year.<sup>14</sup>

- Experts felt that INR value variability and unreliable test values from various labs have led to a discouraging prescribing pattern for dabigatran in Indian scenario.
- They further added that in case the patients are already on antiplatelet therapy with an oral anticoagulant, clopidogrel should be the choice of antiplatelet drug and aspirin should be withdrawn. In patients in whom aspirin needs to be used, the dose should not exceed 75 mg once a day.

### ***Stroke prevention in a pregnant woman with AF***

As per the European Society of Cardiology (ESC) guideline for the management of atrial fibrillation, VKAs should be avoided in the first three months of pregnancy due to their teratogenic potential.<sup>19</sup> Additionally, VKAs should not be given 2-4 weeks before delivery, to avoid any fetal bleeding. Low molecular weight heparins are considered a safer option, as they do not cross the placenta.<sup>19</sup> In the last trimester, frequent monitoring of anticoagulation (i.e. every 10 to 14 days) with corresponding dose adjustments is advised, given that, in some women, high doses of VKAs and heparin might be needed to maintain adequate anticoagulation. Pregnant women with AF and mechanical prosthetic valves who elect to stop VKA treatment in consultation with their physician between six and 12 weeks of gestation, should receive continuous, dose-adjusted unfractionated heparin or dose-adjusted subcutaneous low-molecular-weight heparins.<sup>19</sup>

As limited clinical data are available about the teratogenic potential of NOACs, these agents should be avoided during pregnancy.<sup>19</sup>

The warfarin dose recommended by guidelines in women with or without mechanical valves is  $\leq 5$  mg/day throughout pregnancy; however, during the first trimester, dose-adjusted LMWH is given to avoid teratogenic effects. In pregnant women with a prosthetic valve, dose-adjusted LMWH is initiated at 1mg/kg in the first trimester of pregnancy. In the second and third trimesters, warfarin is continued, and at peripartum, dose-adjusted IV unfractionated heparin/LMWH is recommended.<sup>14</sup>

#### *Key expert opinions*

- More than 70% of the experts had the opinion of switching to a low-dose oral acenocoumarol therapy from dabigatran in cases where dabigatran was already being used before pregnancy. Low-dose acenocoumarol is recommended because dabigatran may cause severe bleeding events and affect the physical and mental growth of the fetus if taken during the last 6 months of pregnancy.

- All the clinical experts unanimously stated that gynecologists being the primary caregivers for pregnant women should be well informed about the anticoagulation protocol in order to avoid any kind of complications.
- Approximately 60% of the experts recommended INR/ PT monitoring frequency to be twice weekly for pregnant women.
- The experts recommended that unfractionated heparin should be administered and continued for the first trimester of pregnancy, followed by low-dose VKA (acenocoumarol or warfarin) therapy up to 36 weeks. After that, low-molecular-weight heparin should be given till 36 hours before the expected delivery.

**Oral anticoagulation therapy in patients with valvular heart disease**

*Antithrombotic therapy in a VHD patient with prosthetic valve implantation*

The American Heart Association/American College of Cardiology (AHA/ACC) 2017 guidelines recommended

antithrombotic therapy in patients with prosthetic heart valves, as shown in Table 1.<sup>20</sup>

*Key expert opinions*

- All the experts were of the opinion that VKAs are the preferred choice of oral anticoagulant in patients with mitral valve replacement surgery.
- Majority of the experts recommended that the duration of the oral anticoagulation therapy should be for a lifetime in case of mechanical valvular replacement and 3-6 months in case a bioprosthetic valve was used.

*Bridging of Antithrombotic Therapy in a VHD Patient Scheduled for Surgery*

A gap in anticoagulation therapy is required in patients with mechanical heart valves scheduled for any surgical or diagnostic procedure. Bridging of anticoagulation should be personalized, with the risks of bleeding weighed against the benefits of thromboembolism. The AHA/ACC 2017 recommendations for bridging are shown in Table 2.<sup>20</sup>

**Table 1: Recommendations for antithrombotic therapy for patients with prosthetic heart valves.<sup>20</sup>**

COR	LOE	Recommendations
I	A	Anticoagulation with a VKA and INR monitoring is recommended in patients with a mechanical prosthetic valve.
I	B	Anticoagulation with a VKA to achieve an INR of 2.5 is recommended for patients with a mechanical bileaflet or current-generation single-tilting disc AVR and no risk factors for thromboembolism.
I	B	Anticoagulation with a VKA is indicated to achieve an INR of 3.0 in patients with a mechanical AVR and additional risk factors for thromboembolic events (AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions) or an older-generation mechanical AVR (such as ball-in-cage).
I	B	Anticoagulation with a VKA is indicated to achieve an INR of 3.0 in patients with a mechanical MVR.
I	A	Aspirin 75 mg to 100 mg daily is recommended in addition to anticoagulation with a VKA in patients with a mechanical valve prosthesis.
IIa	B	Aspirin 75 mg to 100 mg per day is reasonable in all patients with a bioprosthetic aortic or mitral valve.
IIa	B-NR	Anticoagulation with a VKA to achieve an INR of 2.5 is reasonable for at least 3 months and for as long as 6 months after surgical bioprosthetic MVR or AVR in patients at low risk of bleeding.
IIb	B-R	A lower target INR of 1.5 to 2.0 may be reasonable in patients with mechanical On-X AVR and no thromboembolic risk factors.
IIb	B-NR	Anticoagulation with a VKA to achieve an INR of 2.5 may be reasonable for at least 3 months after TAVR in patients at low risk of bleeding.
IIb	C	Clopidogrel 75 mg daily may be reasonable for the first 6 months after TAVR in addition to life-long aspirin 75 mg to 100 mg daily.
III: Harm	B	Anticoagulant therapy with oral direct thrombin inhibitors or anti-Xa agents should not be used in patients with mechanical valve prostheses.

COR: Class of recommendation; LOE: Level of evidence; VKAs: Vitamin K antagonists; INR: International normalized ratio; AVR: Aortic valve replacement; AF: Atrial fibrillation; LV: Left ventricular; MVR: Mitral valve replacement; TAVR: transcatheter aortic valve replacement.

**Table 2: AHA/ACC 2017 recommendations for bridging therapy for prosthetic valves.<sup>20</sup>**

COR	LOE	Recommendations
I	C	Continuation of VKA anticoagulation with a therapeutic INR is recommended in patients with mechanical heart valves undergoing minor procedures (such as dental extractions or cataract removal) where bleeding is easily controlled.
I	C	Temporary interruption of VKA anticoagulation, without bridging agents while the INR is subtherapeutic, is recommended in patients with a bileaflet mechanical AVR and no other risk factors for thrombosis who are undergoing invasive or surgical procedures.
IIa	C-LD	Bridging anticoagulation therapy during the time interval when the INR is subtherapeutic preoperatively is reasonable on an individualized basis, with the risks of bleeding weighed against the benefits of thromboembolism prevention, for patients who are undergoing invasive or surgical procedures with a: 1) mechanical AVR and any thromboembolic risk factor, 2) older-generation mechanical AVR, or 3) mechanical MVR.
Ia	C	Administration of fresh frozen plasma or prothrombin complex concentrate is reasonable in patients with mechanical valves receiving VKA therapy who require emergency noncardiac surgery or invasive procedures.

COR: Class of recommendation; LOE: Level of evidence; VKA: Vitamin K antagonist; INR: International normalized ratio; AVR: Aortic valve replacement; MVR: Mitral valve replacement.

#### Key expert opinions

- The clinical experts opined that among age, gender, co-medication, and type of heart valve prosthesis, the most important deciding factor for temporary interruption of VKAs therapy is the type of heart valve prosthesis.
- The appropriate duration of the re-initiation of anticoagulation therapy which has been stopped during the major surgical procedure should be 12-24 hours after the surgery. However, clinical experts firmly believed that the decision for the re-initiation should be dependent on whether the bleeding has stopped.

#### Anticoagulation management in a patient with a prosthetic valve complication

As discussed, VKAs are the preferred choice of anticoagulant after prosthetic valve complications. However, the management of prosthetic valve complications should be based on the type of complications. Further, special care is warranted in patients with a mechanical valve and various comorbidities, such as thromboembolic events, thrombosis of valve, and bleeding.<sup>21</sup>

Surgery, ultrafractionated heparin use, and fibrinolytic agent therapy are the recommended options for prosthetic heart valve thrombosis. In patients with left prosthetic valve thrombus, with thrombus burden  $\leq 0.8\text{cm}^2$ , fibrinolytics are recommended over surgery.<sup>21</sup> Right-sided thrombosis can be managed by fibrinolytics if there are no contraindications to fibrinolytics. If fibrinolytic therapy is successful, intravenous unfractionated heparin (UFH) is recommended until the patient achieves an INR of 3-4 for

aortic prosthetic and 3.5-4.5 for mitral prosthetic valves. In patients with bleeding complications, VKAs are discontinued and fresh frozen plasma (FFP) or intravenous prothrombin complex concentrate (PCC) administered if required.<sup>21</sup>

#### Key expert opinions

- The clinical experts discussed that there could be several complications of valvular heart surgery, including thromboembolic and bleeding complications, left and/or right ventricular failure, pulmonary hypertension (PAH), arrhythmias, infective endocarditis, and sudden death.
- They unanimously agreed that clinically investigations must assess the presence of any new heart murmur along with ventricular and valvular functions in order to avoid any complication of the prosthetic valve.
- Transthoracic or transesophageal doppler echocardiography must be performed in case of a complication; if the test is not conclusive, cardiac catheterization and coronary angiography must be performed.
- A further consensus was made on the duration of IV anticoagulation therapy required in the patient after thrombolysis in patient with prosthetic valve. Experts recommended duration of re-initiation the anticoagulation can be up to 3 months in cases of partial resolution of the obstruction and 72 hours post-surgery if there is no or sparse hemodynamic improvement.
- Special reference to the elderly population with valvular heart disease was made. This population is at a high thromboembolic and hemorrhagic risk. Assessment of the benefit-risk ratio of anticoagulation therapy should be carefully made with due

considerations to the patient's renal function and comorbidities to maximize the safety profile.

### **Anticoagulation management in patients with stroke**

#### *Anticoagulation management in a patient with a prosthetic valve complication*

Anticoagulation therapy has proven efficacy in reducing the incidence of stroke and systemic embolism in patients with AF and mechanical heart valves. However, the risk of intracranial hemorrhage (ICH) in these patients should be carefully evaluated before initiating anticoagulant therapy.<sup>22</sup> A meta-analysis revealed that re-initiation of anticoagulation therapy is associated with a lower risk of thromboembolic events such as stroke and MI. Moreover, there was no increase in the risk of ICH recurrence with the administration of these anticoagulants.<sup>22</sup>

Aspirin or other antiplatelet agents are used as first-line therapy for the prevention of recurrent stroke in patients with non-cardioembolic stroke. However, in a patient with cardioembolic acute ischemic stroke (AIS) in the setting of AF, oral anticoagulation therapy should be started within 4 to 14 days following the onset of neurological symptoms.<sup>23</sup>

#### *Key expert opinions*

- A total of 54.5% of the clinical experts voted for 3-4 days from ischemic stroke onset as the optimal time to initiate anticoagulant therapy in patients with acute stroke and AF.
- The neurologists added their inputs on the frequency of the CT scan after starting the anticoagulation drug. They added that imaging has to be done 24 hours after the start of anticoagulation therapy. Contrast CT is not advised in acute stroke management except if the aim is CT angiogram. For screening purposes, a non-contrast CT scan is preferable over contrast CT scan.
- A total of 46.7% of the clinical experts voted that cardioversion and aspirin therapy before anticoagulation therapy should be the immediate steps for effective management of the patient.

#### *Anticoagulation therapy in a patient presenting with AIS and AF*

The RAF study revealed that initiating anticoagulant treatment between day 4 and day 14 from AIS is relatively safer and more effective compared with starting treatment before or after this period (Hazard Ratio (HR), 0.53; 95% Confidence Interval (CI), 0.30-0.93 for starting anticoagulation at 4-14 days compared with <4 days).<sup>24</sup> Another study (RAF NOAC) using NOACs instead of VKAs showed that patients who initiated NOACs within two days after an acute stroke had a composite rate of recurrence and major bleeding of 12.4%. The composite rates of recurrence and major bleeding were 2.1% for those

who initiated NOACs between 3 and 14 days and 9.1% for those who initiated treatment >14 days after an acute stroke.<sup>25</sup>

#### *Key expert opinions*

- More than half of the clinical experts voted that VKAs should be advised 1 week or later for the patient, and that early initiation of VKAs is not recommended in the treatment of patients with AIS and metallic prosthetic valves.
- Clinical experts opinionated that IV thrombolysis can be administered if the INR is  $\leq 1.7$ . If large-vessel occlusion is present, mechanical thrombectomy should be performed; in case of a peripheral vessel, intra-arterial thrombolysis should be preferred.

#### *Anticoagulation management in a patient with hemorrhagic stroke*

As per guideline recommendations, patients with ICH whose INR is elevated due to oral anticoagulant, should not be administered anticoagulants; they should be administered therapy to replace vitamin K-dependent factors along with correction of INR. Glucose levels should be monitored; also, if they present with clinical seizures, they should be treated with antiepileptic drugs.<sup>26</sup>

Patients with cerebellar hemorrhage who are degrading neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage at the earliest. Additionally, post-acute ICH, blood pressure (BP) should be well controlled, particularly for patients with ICH location typical of hypertensive vasculopathy.<sup>26</sup>

#### *Key expert opinions*

- More than 80% of the clinical experts recommended that BP management and initiation of the anticoagulation at 7-10 days post-ictus should be the strategy to manage the patient.
- The experts emphasized on the importance of BP management in an ischemic patient and highlighted that labetalol is frequently used in clinical practice.

### **Anticoagulation management in patients with stroke**

#### *Management of DVT in a patient with renal impairment*

Patients with chronic kidney disease (CKD) represent a special subpopulation, and they represent a high-risk group for thrombosis in the cardiovascular system and venous circulation. Presently, options for this subgroup are unfractionated heparin, LMWHs (including fondaparinux), and VKAs.<sup>27-29</sup> Dabigatran, and to a lesser extent, rivaroxaban and apixaban are excreted through the kidneys; as a result, the anticoagulant effect is accentuated

through drug accumulation in renal disease patients. Hence, the recent AHA/ACC guideline recommends VKA as the preferred choice in patients with advanced CKD or end-stage renal disease. The greater the renal function decline in a patient, the lower the advantage offered by new agents over VKAs.<sup>27-29</sup>

#### Key expert opinions

- All the experts recommended that direct oral anticoagulants (DOACs) should be used cautiously in patients with acute and chronic kidney disease, as these drugs are partially eliminated by the kidneys and can potentially increase the bleeding risk in patients with CKD. In patients on DOACs, renal function needs to be monitored meticulously, at least yearly, to detect changes in renal function and adjust the dose accordingly.
- Experts believed that low-molecular heparin and VKAs are the choice of drugs in patients with renal dysfunction. The patient should be carefully selected through the use of risk stratification scores (CHA<sub>2</sub>DS<sub>2</sub>-VAsc and Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly [HAS-BLED] scores), and once oral anticoagulation is initiated, ensure that steps are taken to reduce bleeding risk and regular monitoring of renal function if a DOAC is chosen, to allow for dose alteration as needed
- Majority of the experts favored quantitative D-dimer assay approach for the patient, despite the literature supporting that both qualitative and quantitative assays would yield more appropriate results in the patient.
- Clinical experts advocated that regular monitoring of PT/INR levels in patients on VKAs must be done to regulate the correct therapeutic dose.

#### Anticoagulation management in a patient with unprovoked DVT

There is still uncertainty about the optimal management of patients with unprovoked VTE. These patients comprise approximately half of all patients with a first VTE. In patients receiving three months of anticoagulation therapy, the risk of recurrent VTE ranges between 5% and 15 % per year after therapy is stopped. This risk increases to 30%-35 % after five years, and this recurrence risk is unaffected by whether patients receive an additional 3-9 months of anticoagulation therapy.<sup>30,31</sup>

#### Key expert opinions

- Approximately 54% of the clinical experts considered initiation of anticoagulation therapy and clot removal by catheter-directed thrombolysis and thrombectomy as the appropriate management strategies in the patient with unprovoked DVT.

- Eighty-five percent of the clinical experts preferred using Well's score to assess the risk of recurrence in the patient.
- Majority of the experts recommended an indefinite period of treatment for the patient. Although clinical data indicate that if patients with a first unprovoked proximal DVT or PE are not treated indefinitely, then the anticoagulants are stopped at 3 rather than 6 months.
- Experts recommended compression therapy; however, this therapy cannot be continued for a longer duration because of poor patient compliance.
- All the experts unanimously recommended that anticoagulation clinics would be helpful in improving patient adherence and emphasized on patient education regarding the importance of follow-up, to further reduce the risk of DVT.

#### CONCLUSION

Vitamin K antagonists such as warfarin and acenocoumarol still dominate the Indian anticoagulation therapy landscape. Despite having numerous advantages such as less frequent monitoring and low risk of intracranial or intracerebral bleeding, NOACs such as dabigatran are not widely used in the Indian clinical scenario. The selection of an oral anticoagulant agent in India is influenced by the economic status of patients and the presence of comorbidities.

Physicians thus prefer to prescribe cost-effective VKAs instead of NOACs. Maintaining an optimum INR/PT level is the key to effectively manage patients on oral anticoagulation therapy. However, in India, major challenges are: lack of standard clinical recommendations for various populations, standardized measurement of PT/INR, and patient education—all of which reduce therapy compliance. Additionally, there is a huge burden of stroke in India, and the prevalence rate is higher in urban areas than in rural areas. Anticoagulation therapy reduces the incidence of stroke and systemic embolism in patients with AF and mechanical heart valves. Clinical recommendations for anticoagulation therapy in the Indian population are the need of the hour. Key opinions of the panelists, enumerated as key expert opinions in this article, can assist clinicians in charting out a pathway to diagnose and treat patients with thrombotic diseases in the Indian setting.

#### ACKNOWLEDGMENT

Writing assistance was provided by Dr. Kavitha Ganesh, BioQuest Solutions.

Authors gratefully acknowledge the contribution of experts across India who gave their expert opinions for the

conceptualization and finalization of consensus statements in the advisory board meetings:

Dr. Rajan Joseph Manjuran, Dr. Soumitra Kumar, Dr. Subhash Chandra, Dr. Manjinder Sandhu, Dr. Tarun Grover, Dr. BK Mahala, Dr. Arunangshu Ganguly, Dr. KA Sambasivam, Dr. KM Mandana, Dr. Sanjay Dhaded, Dr. Ummer K., Dr. Abhijit Pathak, Dr. SK Aggarwal, Dr. Rakesh Kumar Singh, Dr. Shailendra, Dr. Vikram Goyal, Dr. Yogendra Singh, Dr. RP Singh, Dr. Prashant Vaijyanath, Dr. B Kesavamoorthy, Dr. S Selvamani, Dr. G Elangovan, Dr. K Damodhar Rao, Dr. C. Chandra Shekar, Dr. Sanjay Kumar, Dr. Kashif Syed, Dr. Nirmal Kumar, Dr. Hemang Baxi, Dr. Vijay Thakore, Dr. Mukesh Parikh, Dr. Rakesh Gupta, Dr. Ajay K., Dr. Ramesh Kavar.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: Not required*

## REFERENCES

- Amin A, Marrs JC. Direct oral anticoagulants for the management of thromboembolic disorders: The importance of adherence and persistence in achieving beneficial outcomes. *Clin Appl Thromb.* 2016;22(7):605-16.
- Trailokya A, Hiremath JS, Sawhney J, Mishra YK, Kanhere V, Srinivasa R, et al. Acenocoumarol: A review of anticoagulant efficacy and safety. *J Assoc Physicians India.* 2016;64:88-93.
- Cheng JW, Barillari G. Non-vitamin K antagonist oral anticoagulants in cardiovascular disease management: Evidence and unanswered questions. *J Clin Pharm Ther.* 2014;39(2):118-135.
- Zirlik A, Bode C. Vitamin K antagonists: relative strengths and weaknesses vs. direct oral anticoagulants for stroke prevention in patients with atrial fibrillation. *J Thromb Thrombolysis.* 2017;43(3):365-379.
- Scaglione F. New oral anticoagulants: Comparative pharmacology with vitamin K antagonists. *Clin Pharmacokinet.* 2013;52(2):69-82.
- Mekaj A, Mekaj Y, Duci S, Miftari E. New oral anticoagulants: Their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. *Ther Clin Risk Manag.* 2015;11:967.
- Dalal JJ, Dhall A, Bhave A. Current perspective on use of NOAC in clinical practice in India. *J Assoc Physicians India.* 2016;64:56-65.
- Carmo J, Costa FM, Ferreira J, Mendes M. Dabigatran in real-world atrial fibrillation: Meta-analysis of observational comparison studies with vitamin K antagonists. *Thromb Haemost.* 2016;116(4):754-63.
- Parakh R, Krishna PR, Amin P, Bedi VS, Desai S, Dumra HS, et al. Consensus on management of deep vein thrombosis with emphasis on NOACs (Non-vitamin K antagonist oral anticoagulants): Recommendations from inter-disciplinary group of Indian experts. *J Assoc Physicians India.* 2016;64(9):7-26.
- Current Indian scenario on the use of oral anticoagulants. *J Assoc Physicians India.* 2014;62(6):28-9.
- Asinger RW, Shroff GR, Simegn MA, Herzog CA. Anticoagulation for Nonvalvular Atrial Fibrillation. *Circ Cardiovasc Qual Outcom.* 2017;10(9):e003669.
- Matiasz R, Rigolin VH. 2017 focused update for management of patients with valvular heart disease: Summary of new recommendations. *J Am Heart Assoc.* 2018;7(1):1-17.
- D'Souza R, Ostro J, Shah PS, Silversides CK, Malinowski A, Murphy KE, et al. Anticoagulation for pregnant women with mechanical heart valves: A systematic review and meta-Analysis. *Eur Heart J.* 2017;38(19):1509-16.
- Alshawabkeh L, Economy KE, Valente AM. Anticoagulation During Pregnancy: Evolving Strategies With a Focus on Mechanical Valves. *J Am Coll Cardiol.* 2016;68(16):1804-13.
- Feigin VL, Norrving B, Mensah GA. Global Burden of Stroke. *Circ Res.* 2017;120(3):439-448.
- Pandian JD, Sudhan P. Stroke epidemiology and stroke care services in India. *J stroke.* 2013;15(3):128-34.
- Kamerkar DR, John MJ, Desai SC, Dsilva LC, Joglekar SJ. Arrive: A retrospective registry of Indian patients with venous thromboembolism. *Indian J Crit Care Med.* 2016;20(3):150.
- Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation.* 2014;129(7):764-72.
- Kirchhof P, Benussi S, Kotecha D, Kotecha D, Ahlsson A, Atar D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J.* 2016;37(38):289362.
- Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2017;70(2):252-89.
- Saksena D, Muralidharan S, Mishra YK, Kanhere V, Mohanty BB, Srivastava CP, et al. Anticoagulation Management in Patients with Valve Replacement. 2018;66:59-74.
- Murthy SB, Gupta A, Merkler AE, Navi BB, Mandava P, Iadecola C, et al. Restarting anticoagulant therapy after intracranial hemorrhage: A systematic review and meta-analysis. *Stroke.* 2017;48(6):1594-600.



23. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2018;49(3):e46-e110
24. Paciaroni M, Agnelli G, Falocci N, Caso V, Becattini C, Marcheselli S, et al. Early recurrence and cerebral bleeding in patients with acute ischemic stroke and atrial fibrillation: Effect of anticoagulation and its timing: The RAF study. *Stroke.* 2015;46(8):2175-82.
25. Paciaroni M, Agnelli G, Falocci N, Tsivgoulis G, Vadikolias K, Liantinioti C, et al. Early recurrence and major bleeding in patients with acute ischemic stroke and atrial fibrillation treated with Non-Vitamin-K oral anticoagulants (RAF-NOACs) Study. *J Am Heart Assoc.* 2017;6(12):1-14.
26. Morgenstern LB, Hemphill JC, Anderson C, Becker K, Broderick JP, Connolly Jr ES, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2010;41(9):2108-29.
27. Hughes S, Szeki I, Nash MJ, Thachil J. Anticoagulation in chronic kidney disease patients- the practical aspects. *Clin Kidney J.* 2014;7(5):442-9.
28. J. Lutz, K. Jurk, H. Schinzel. Direct oral anticoagulants in patients with chronic kidney disease: Patient selection and special considerations. *Int J Nephrol Renovasc Dis.* 2017;10:135-43.
29. Chan KE, Giugliano RP, Patel MR, Abramson S, Jardine M, Zhao S, et al. Nonvitamin K Anticoagulant Agents in Patients With Advanced Chronic Kidney Disease or on Dialysis With AF. *J Am Coll Cardiol.* 2016;67(24):2888-99.
30. Marcucci M, Iorio A, Douketis J. Management of patients with unprovoked venous thromboembolism: An evidence-based and practical approach. *Curr Treat Options Cardiovasc Med.* 2013;15(2):224-39.
31. Moodley O, Goubran H. Should lifelong anticoagulation for unprovoked venous thromboembolism be revisited? *Thromb J.* 2015;13(1):1-9.

**Cite this article as:** Menon A, Thomas J, Ichaporia NR, Sahoo PK, Unni TG. Oral anticoagulation therapy: current challenges in Indian scenario. *Int J Adv Med* 2020;7:1044-52.