Introduction And Background

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia encountered in clinical practice [1]. The estimated global prevalence of AF in 2010 was reported to be nearly 33.5 million individuals [2]. The World Heart Federation (WHF) in its 2020 update of the “Roadmap” initiative reported the prevalence of AF in India to be between 0.1% and 0.5% in the general population for the period of 2001-2010. The prevalence for the general population aged >75 years [3]. The Indian Heart Rhythm Society (IHRs) AF registry revealed that Indian patients with AF are more than a decade younger than those in the Western world. The underlying cause in Indian patients was determined to be rheumatic valvular heart disease (RHD), followed by hypertension, diabetes, and coronary artery disease [4].

AF is associated with substantial mortality and morbidity from stroke and thromboembolism [5]. AF patients pose a five-fold higher risk of stroke [6]. The mortality associated with ischemic stroke can be nearly twice in patients with AF as compared to those without AF [7]. Traditionally, vitamin K antagonists (VKA), especially warfarin were the preferred anticoagulants. But due to their many limitations including narrow therapeutic window, need for regular monitoring, slow onset of action, and numerous drug and food interactions, novel oral anticoagulants (NOACs) have evolved as the preferred agents. The NOACs provide a rapid onset of action, no need for routine laboratory monitoring, and a significantly lower risk of bleeding compared to VKAs [8]. The authors in this review aim to identify the main points for the CPs to identify AF and initiate anticoagulation in patients with non-valvular AF (NVAF) and bring to the table a simplified recommendation supported by expert opinion and guidelines for stroke prevention in NVAF patients.
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All the experts who were invited for the preceding advisory board are of ~20 to 30 years of clinical experience in the management of NVAF and are very well aware of the evolving landscape of anticoagulants. Their expert opinion was weighed along with the evidence from the literature including the recommendations from the guidelines to propose the protocol for the management of stroke prevention in AF suitable for the primary care setting in India.

**Review**

**Recent guidelines**

Various clinical practice guidelines have provided recommendations for the prevention of stroke in patients with AF. The recommendations made by the 2019 American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society (AHA/ACC/HRS Focused Update of the latest AHA/ACC/HRS Guideline) [11], the 2020 European Society of Cardiology (ESC) [12], and the 2021 European Heart Rhythm Association Practical Guide [13] are summarized in Table 1.

**Guideline recommendations**

| Anticoagulants are recommended                                                                 | In AF patients, oral anticoagulants are recommended when a CHA₂DS₂-VASc score of ≥2 in men or ≥3 in women. (Level of evidence: I; strength of recommendation: A) |
|-----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| NOACs are preferred over warfarin in NOAC-eligible patients with AF (exception: patients with “moderate-to-severe mitral stenosis or a mechanical heart valve”) |                                                                                                                                                                                                 |
| Choice of OACs should be based on thromboembolism risk, irrespective of the AF pattern        |                                                                                                                                                                                                 |
| Evaluate renal function and hepatic function before starting NOAC therapy and should be reevaluated at least once a year |                                                                                                                                                                                                 |
| Reevaluate the need for and choice of anticoagulant therapy periodically                      |                                                                                                                                                                                                 |
| Reassess stroke and bleeding risks                                                           |                                                                                                                                                                                                 |
| Use of antiplatelet monotherapy or aspirin-clopidogrel combination is discouraged             |                                                                                                                                                                                                 |

| Pointers to be noted before initiating anticoagulants                                         | Patients with mechanical prosthetic valve and moderate to severe mitral stenosis                                                                                                                |
|-----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Reevaluate the need for and choice of anticoagulant therapy periodically                       | Patients with bioprosthetic valve can be anticoagulated with NOACs only if it is degenerative mitral regurgitation or if the valve is in the aortic position |
| Reassess stroke and bleeding risks                                                           | Patients with hypertrophic cardiomyopathy can be considered for NOAC treatment but the data is limited                                    |
| Use of antiplatelet monotherapy or aspirin-clopidogrel combination is discouraged             |                                                                                                                                                                                                 |

**TABLE 1: Summary of guidelines**

AF: atrial fibrillation; CHA₂DS₂-VASc: congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65-74, and sex (female); INR: international normalized ratio; NOAC: novel oral anticoagulants; OAC: oral anticoagulation; VKA: vitamin K antagonists

The table is adapted from the 2019 American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society (AHA/ACC/HRS Focused Update of the latest AHA/ACC/HRS Guideline) [11], the 2020 European Society of Cardiology (ESC) [12], and the 2021 European Heart Rhythm Association Practical Guide [13].

**Protocol for consulting physicians**

**Screening**

In 20–45% of stroke cases, the underlying AF is detected at the time of stroke. The reason for under-detection of AF can be because of a significant proportion of cryptogenic strokes attributed to undetected AF. AF remains asymptomatic in almost one-third of the cases and most of the symptomatic patients have atypical symptoms [14]. Paroxysmal AF can progress to sustained forms of AF within the first year and the progression rate ranges from 8.6% to 15% [15]. Unattended sustained AF has a high risk of stroke and heart failure (HF). Hence, for many patients, the steps required to prevent sustained AF should begin early. Stroke is preventable with a 66% reduction in risk when appropriate anticoagulation therapy is given to eligible patients with AF. Hence screening of patients for AF is vital to prevent stroke in patients [14]. The conventional risk factors for AF include coronary heart disease, hypertension, heart failure, left
ventricular diastolic dysfunction, diabetes, hyperthyroidism, obesity, and valvular heart disease [16]. The experts in the advisory board opined that CPs should assess the high-risk patients for AF and can follow a checklist to identify patients (Figure 1). The panelists suggested that if the electrocardiogram (ECG) is normal, the patients should be followed up for their primary condition for which they visited. The CPs can consider doing echocardiography if the patient has cardiac co-morbidities.

| 1. Age |
| >65 years |

| 2. Co-morbidities |
| Diabetes |
| Hypertension |
| Hyperthyroidism |
| Chronic Kidney Disease (CKD) |
| Valvular heart disease |
| Left ventricular dysfunction |
| Ischemic heart disease |
| Peripheral arterial disease |
| Heart failure |

| 3. ECG assessment |
| Normal |
| (Further follow-up to be done if AF detected is required; refer algorithm) |

**FIGURE 1: Panel recommendations for screening of high-risk patients for AF**

AF: atrial fibrillation; CKD: chronic kidney disease; ECG: electrocardiogram

**Diagnosis**

AF is suspected when an irregular pulse is observed in a patient and must be confirmed using a 12-lead ECG [17]. The diagnosis of AF requires documentation of ECG recorded cardiac rhythm showing the typical pattern of AF where one episode lasts for at least 30 seconds. When clinical suspicion of atrial fibrillation persists despite normal ECG, a Holter monitor (24-hour recording) or event monitor (seven to 30-day recording) may be warranted [17]. There are five types of AF identified based on the presentation, duration, and spontaneous termination of AF episodes (Table 2) [12]. The anticoagulation strategy however does not depend upon the type of AF.
| Sr. no. | Type of AF                  | Presentation                                                                 |
|--------|----------------------------|-------------------------------------------------------------------------------|
| 1.     | First diagnosed AF         | Previous diagnosis not established regardless of AF duration or severity     |
| 2.     | Paroxysmal AF              | AF episodes that terminate within 7 days (spontaneously or with cardioversion) |
| 3.     | Persistent AF              | AF episode lasting for more than 7 days. This definition is inclusive of episodes terminated by cardioversion (with drugs or by direct current cardioversion) after 7 days or more |
| 4.     | Long-standing persistent AF| AF which continues for >12 months before rhythm control is implemented        |
| 5.     | Permanent AF               | AF accepted by both: the patient and the physician; rhythm control not implemented. |

**TABLE 2: Types of atrial fibrillation**

AF: atrial fibrillation

The table is adapted from Hindricks et al., (2021; ESC 2020) [12].

**Management**

The congestive heart failure, hypertension, age >75 (doubled), diabetes, stroke (doubled), vascular disease, age 65-74, and sex (female) (CHA₂DS₂-VASc) score is used to identify the risk of thromboembolism in AF patients and hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol (HAS-BLED) score assesses the risk of bleeding in anticoagulation (Table 3) [18,19].
**Stroke risk factors**

| CHA2DS2-VASc score                              | Score |
|------------------------------------------------|-------|
| Congestive heart failure/LV dysfunction        | 1     |
| Hypertension                                   | 1     |
| Aged ≥ 75 years                                 | 2     |
| Diabetes mellitus                              | 1     |
| Stroke/ TIA/ TE                                | 2     |
| Vascular disease (prior MI, PAD, or aortic plaque) | 1     |
| Aged 65-75 years                               | 1     |
| Sex category (i.e., female gender)             | 1     |
| Maximum score                                  | 9     |

**HAS-BLED score**

| Hypertension, i.e., uncontrolled BP            | 1     |
| Abnormal renal/liver function                 | 1 or 2|
| Stroke                                        | 1     |
| Bleeding tendency or predisposition           | 1     |
| Labile INR                                     | 1     |
| Age (e.g., > 65)                               | 1     |
| Drugs (e.g., concomitant aspirin or NSAIDs) or alcohol | 1     |
| Maximum score                                  | 9     |

**Has-Bled score of ≥3 warrants for regular clinical review and follow-up**

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**TABLE 3: Calculation of CHA2DS2-VASc score and HAS-BLED score**

*HAS-BLED score of ≥3 warrants regular clinical review and follow-up.*

CHA2DS2-VASc: congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65-74, and sex (female); HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol; PAD: peripheral arterial disease; MI: myocardial infarction; TIA: transient ischemic attack; TE: transesophageal echocardiography; LV: left ventricular; BP: blood pressure; INR: international normalized ratio; NSAIDs: non-steroidal antiinflammatory drugs

The table is adapted from CHA2DS2-VASc 1 [18] and HAS-BLED Tool (2012) [19].

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**Evolution of treatment**

The management strategies for stroke prevention have evolved substantially in the past three decades. Novel drugs have been developed and robust clinical studies and meta-analyses have supported the use of anticoagulants for stroke prevention. Some of the landmark events in the evolution of stroke prevention management have been presented in Figure 2 [12,20].
Issues with warfarin

Warfarin, a vitamin K antagonist is the most widely used anticoagulant. However, in the recent past, its use for the same has decreased due to many challenges including unreliable INR values, unpredictable outcomes, and need for continuous monitoring and availability of NOACs [21]. Warfarin loading doses may result in a hypercoagulable state and potential clot formation because of significant reductions in protein C and protein S levels (Table 4) [22].

| Limitations of VKA | Implications on clinical practice* | Advantages of NOACs |
|--------------------|-----------------------------------|---------------------|
| Risk of bleeding complications, including intracranial hemorrhage | Increased hospital cost, increased hospitalization rate, increased mortality | Lower incidence of major bleeding |
| Routine monitoring required | Increased laboratory cost, increased hospital visits | Convenience of use, no need for laboratory monitoring |
| Dose adjustments frequently needed | Increased hospital visits | NOACs are administered in fixed doses, except when a patient has a disorder of the liver or kidney |
| Slow onset of action | Increased risk of stroke | Rapid onset and offset of action, a short half-life |
| Narrow therapeutic window | Increased risk of stroke and bleeding | Wide therapeutic window |
| Dietary restrictions Numerous drug interaction | Reduced adherence, increased risk of stroke and bleeding | Fewer drug and food interactions |
| Variability in patient response | Difficulty in standardized approach and frequent follow-ups | Less variability |

TABLE 4: Advantages of NOACs over VKA in the management of stroke prevention in patients with AF

The table mentions the limitations of VKA in stroke prevention in AF patients and its implications on clinical practice which are addressed by the NOACs [23,24].

*As per the expert opinion.

AF: atrial fibrillation; NOAC: novel oral anticoagulant; VKA: vitamin K antagonists

In a meta-analysis by Ruff et al., the safety and efficacy of NOACs were compared to warfarin in patients with atrial fibrillation. NOACs were associated with a reduced composite of stroke or systemic embolic events by 19% as compared with warfarin. There was also a reduction in major bleeding by 14% with NOACs [25]. In the Anticoagulants for Reduction in Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients [26].
Outcomes and Experience of Patients (ARISTOPHANES) study, warfarin was reported to have a higher stroke/systemic embolism rate as compared to apixaban (1.92 vs. 1.33 per 100 person-years), dabigatran (1.74 vs. 1.44 per 100 person-years), and rivaroxaban (1.90 vs. 1.51 per 100 person-years). Apixaban (hazard ratio [HR], 0.60; 95% confidence interval [CI], 0.56-0.63) and dabigatran (HR, 0.71; 95% CI, 0.65-0.78) were associated with lower rates of major bleeding as compared to warfarin, while rivaroxaban (HR, 1.06; 95% CI, 1.02-1.10) had a higher rate of major bleeding compared with warfarin [26]. Apixaban was associated with fewer major bleeds in comparison to all other NOACs. Figure 3 depicts the checklist for CPs designed based on the expert opinion of the advisors.

| Sr. No. | Checkpoint |  |  |  |
|---------|------------|---|---|---|
| 1.      | NVAF diagnosed | ☐ | ☐ | N |
| 2.      | CHA₂DS₂-VASc score | ☐ | ☐ | N | Score:  |
| 3.      | HAS-BLED score | ☐ | ☐ | N | Score:  |
| 4.      | Concomitant Medications | ☐ | ☐ | N | List of concomitant medications:  |
| 5.      | Comorbidities |  |  |  |
|         | Renal Impairment | ☐ |  |  |
|         | Diabetes | ☐ |  |  |
|         | Heart Failure | ☐ |  |  |
|         | Myocardial Infarction | ☐ |  |  |
|         | Mechanical Heart Valve | ☐ |  |  |
|         | Rheumatic Heart Disease | ☐ |  |  |
|         | Any Coagulation Disorder | ☐ |  |  |
|         | Prior Stroke/ TIA | ☐ |  |  |
|         | Prior History of Bleeding | ☐ |  |  |
| 6.      | Creatinine Clearance | ☐ | ☐ | N | Value:  |
| 7.      | Weight | ☐ | ☐ | N | Value: _________ kgs  |
| 8.      | Age | ☐ | ☐ | N | Value: _________ years  |
| 9.      | Is ECHO done | ☐ | ☐ | N | Findings:  |
| 10.     | Prior bleeding | ☐ | ☐ | N |  |
| 11.     | Patients to be referred to specialists: |  |  |  |
|         | 1. > 80 years of age |  |  |  |
|         | 2. Chronic kidney disease (CKD) |  |  |  |
|         | 3. Valvular heart disease |  |  |  |
|         | 4. Ischemic Heart Disease |  |  |  |
|         | 5. Low ejection fraction |  |  |  |

FIGURE 3: Checklist for CPs before initiating OAC therapy or referring to a specialist

CKD: chronic kidney disease; ECHO: echocardiogram; MI: myocardial infarction; NVAF: non-valvular atrial fibrillation; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; TIA: transient ischemic attack

Tailor-Made Therapy

Elderly and very elderly: Elderly patients (age above 75 years) [27] are more prone to thromboembolic events as well as have an increased risk of bleeding [28]. The factors apart from age that are responsible for venous thromboembolism (VTE) include the presence of comorbid conditions, increased risk of falls, renal insufficiency, potential drug interactions, and dementia [27]. The Fit FOR The Aged (FORTA) list is a drug classification combining positive and negative labeling of drugs frequently prescribed to elderly patients [29]. As per the consensus, apixaban has been rated as FORTA "A" (i.e., A bsolutely = indispensable)
drug, clear-cut benefit in terms of efficacy/safety ratio proven in elderly patients for a given indication), while warfarin, dabigatran, and rivaroxaban are given FORTA B label (i.e., B-eneficial – drugs with proven or obvious efficacy in the elderly, but limited extent of effect or safety concerns) [30].

**Renal impairment**

Patients with chronic kidney disease (CKD) are at two to three times higher risk of developing AF as compared to the general population. The risk of thromboembolism due to AF in CKD patients is independently higher as compared to those without CKD [31-33].

The NOACs are eliminated renally to varying extent and hence dose adjustment is warranted to manage the risk of bleeding. The calculation of dose reduction is critical as either efficacy or safety is affected with inappropriate doses [34]. Warfarin has been reported to cause renal damage in patients with CKD and is also associated with the progression of renal disease [35]. Apixaban is approved for patients with creatinine clearance <15 mL/min including dialysis for all indications in India [36]. The dosing of NOACs based on stages of CKD has been depicted in Figure 4 [36-40].

**Impaired hepatic function**

NOACs undergo significant metabolism in the liver. Hepatic impairment thus may lead to an increase in drug levels and decrease in coagulation factors and may result in consequent bleeding. Some NOACs are dependent on cytochrome P450 enzymes for metabolism and in case of hepatic impairment, the activity of these enzymes may be altered. Hence, dose adjustment in patients with hepatic impairment is warranted (Figure 5) [41].
Patients with increased risk of GI bleeding

Dabigatran and rivaroxaban are associated with more than 50% and more than a two-fold increased risk of gastrointestinal (GI) bleeding, respectively, when compared to warfarin [42]. Apixaban has been shown to have comparable major GI bleeds to warfarin. For patients at high risk of GI bleeding, ESC 2016 recommends the use of VKA or NOAC other than dabigatran 150 mg or rivaroxaban 20 mg (class IIa, level B) [20].

Extreme low body weight

The efficacy of NOACs is directly correlated to their plasma concentrations. Since the distribution volume is linked to body weight, extreme body weight can affect their efficacy or safety. Recommendations for dose adjustment based on body weight are represented in Table 5 [43].

| NOAC               | Lower body weight allowed | Upper body weight allowed | Recommended dose adjustment                      |
|--------------------|----------------------------|----------------------------|--------------------------------------------------|
| Dabigatran etexilate | 50 kg                      | 110 kg                     | No dose adjustment necessary                      |
| Rivaroxaban        | None                       | None                       | No dose adjustment necessary                      |
| Apixaban           | None                       | None                       | No dose adjustments required unless ABC criteria are met. |

TABLE 5: Dose adjustment for NOACs based on body weight

NOACs: novel oral anticoagulants

The table is adapted from De Caterina and Lip (2017) [43].

Minor procedures

The EHRA has put together recommendations for temporarily discontinuing anticoagulants for patients undergoing minor invasive procedures (Figure 6) [13,44]. Due to the increased risk of bleeding, anticoagulant therapy may require temporary cessation in some patients. The conditions and timings for cessation and re-initiating anticoagulants depend on the type of procedure and patient characteristics.
FIGURE 6: Use of anticoagulants in case of minor procedures

NOACs can be resumed six to eight hours after the end of the intervention.

*Including cardiac device implantations.

**A graded interruption should be considered for patients on dabigatran and a CrCl <80 mL/min.

***Twenty-four hours before in patients with normal kidney function.

****With complete hemostasis.

NOACs: novel oral anticoagulants

The figure is adapted from Steffel et al. (2021; EHRA Practical Guide).

The decision of when to stop the NOACs therapy before the invasive procedure is dependent on renal function, type of surgery, and the risk of bleeding. In case a minor surgical intervention which is associated with minimal bleeding risk and/or adequate local hemostasis can be practiced, NOAC therapy can be restarted after six hours. Recommendations regarding restarting NOACs after invasive procedures with low-risk or high-risk bleeding are presented in Table 6.[45]

| CrCl     | Dabigatran | Apixaban, rivaroxaban |
|----------|------------|-----------------------|
|          | Low risk   | High risk             | Low risk | High risk |
| ≥80 mL/min | ≥24 h      | ≥48 h                 | ≥24 h    | ≥48 h     |
| 50–79 mL/min | ≥24 h      | ≥48 h                 | ≥24 h    | ≥48 h     |
| 30–49 mL/min | ≥48 h      | ≥96 h                 | ≥24 h    | ≥48 h     |

TABLE 6: Last intake of NOACs before an invasive procedure

CrCl: creatinine clearance; NOACs: novel oral anticoagulants

The table is adapted from Chiang et al. (2017)[45].

Caution should be exercised while using NOACs, especially in patients with co-morbidities. The recommendations for the tailor-made for individual patients with NVAF are summarized in Table 7.[27,36,46].
Recommendation

Prior to beginning NOAC therapy, patient’s cognitive function, level of dependence, mobility, possible issues with drug compliance, and risk of falls must be assessed

Avoid multiple medications wherever possible

If a patient is taking non-steroidal antiinflammatory drugs (NSAIDs) switch to another analgesic

Renal function should be checked before initiating NOAC therapy and thereafter at least once every 8-12 months

Dose adjustments for specific NOACs should be made depending on the patient’s age, body weight, and renal function

Patients with high risk of gastrointestinal (GI) bleeding

First choice: for patients with a high risk of gastrointestinal bleeding, apixaban 5 mg twice daily or dabigatran 110 mg twice daily may be used; second choice: dabigatran 150 mg twice daily, or rivaroxaban 20 mg once daily

Patients with renal impairment

First choice: patients with AF and stage III CKD (creatinine clearance 30–49 mL/min) may be treated with apixaban 5 mg twice daily (apixaban 2.5 mg twice a day if ≥1 additional criteria: age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dL (133 mmol/L are present), rivaroxaban 15 mg daily; second choice: dabigatran 110 mg twice daily; not recommended: dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily

Elderly patients

First choice: in patients older than 75 years, we suggest apixaban 5 mg twice daily (2.5 mg if ≥2 of the following: age ≥80 years, body weight ≤60 kg, or creatinine ≥1.5 mg/dL (133 mmol/L)); second choice: dabigatran 110 mg twice daily, or rivaroxaban 20 mg once daily

Previous history of stroke

First choice: NOACs are preferred over warfarin for secondary stroke prevention in patients with AF

Management of bleeding

The panelists of the advisory board also opined that CPs who are treating AF patients with oral anticoagulants (OACs) in case of a bleeding event should immediately stop the anticoagulant, look for potential drug-drug interactions, and refer the patients to a specialist.

The factor concentrates recommended for the management of bleeding due to NOACs include prothrombin complex concentrate (PCC) and activated PCC (aPCC) [13]. For the reversal of direct NOACs, the DCGI has approved one specific antidote: idarucizumab for dabigatran (Figure 7).
**FIGURE 7: Management of bleeding in patients taking NOAC**

| Patient type                                      | Interval                      |
|--------------------------------------------------|-------------------------------|
| Patients other than those specified below        | Yearly                        |
| ≥ 75 years (especially if on dabigatran) or frail | 4-monthly                     |
| If renal function CrCl ≤60mL/min: recheck interval = CrCl/10 months | x-monthly                     |
| If intercurrent condition may impact renal or hepatic function | If needed                    |

**TABLE 8: Follow-up of AF patients on NOACs**

AF: atrial fibrillation; NOAC: novel oral anticoagulant

The table is adapted from Steffel et al. (2021; EHRA Practical Guide 2021) [13].
FIGURE 8: Checklist for patient counseling

NSAID: non-steroidal antiinflammatory drug; OAC: oral anticoagulant; OTC: over-the-counter

Switching

Switching from one oral anticoagulant therapy to another is decided by the treating physician and is dependent on the patient’s eligibility [49]. The major reason for switching from a VKA to a NOAC was occurrence of stroke. Occurrence of myocardial infarction or gastrointestinal bleeding after NOAC initiation significantly increased the chances of switching to VKA. The likelihood of switching from one NOAC to another increased in case of stroke, myocardial infarction, and gastrointestinal bleeding [50]. Ensuring continuous anticoagulant therapy with minimal bleeding risk is paramount while switching between therapies (Figure 9) [13,44].

FIGURE 9: Switching between therapies

*Continue NOAC if INR <2 (half dose if on edoxaban), start VKA (loading dose usually used for phenprocoumon). Continue intensive INR sampling for one month, goal: ≥3 consecutive INR values between 2.0 and 3.0. Edoxaban is not approved in India.

INR: international normalized ratio; NOAC: novel oral anticoagulant; VKA: vitamin K antagonists

The figure is adapted from Steffel et al. (2021; EHRA Practical Guide) [13].

Algorithm
The experts who participated in the advisory board meeting suggested the development of a simplified algorithm that CPs can prevent stroke in AF patients. The algorithm provides a comprehensive summary of how to screen, diagnose, manage, and refer patients. The algorithm has been developed based on treatment guidelines, scientific literature, and clinical experience of the experts (Figure 10).

**FIGURE 10: Algorithm for stroke prevention in AF patients**

*Additionally assess HAS-BLED score

AF: atrial fibrillation; AHRE: atrial high-rate episode; bpm: beats per minute; CHA2DS2-VASc: congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65-74, and sex (female); CKD: chronic kidney disease; ECG: electrocardiogram; HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol

**Conclusions**

The CPs being the primary point of contact for patients, need to be equipped for taking quick decisions regarding the need, choice, and dose of oral anticoagulants to reduce the risk of stroke/systemic embolism in patients with NVAF. In the advisory board convened, the experts came up with a simplified protocol based on the current guidelines of stroke prevention completed with simple checklists as ready reckoner for CPs to
The ultimate goal is to empower the CPs to prescribe NOACs to patients with NVAF.

**Additional Information**

**Disclosures**

*Conflicts of interest:* In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All the authors declare that they received an honorarium as per the fair market value (FMV) from Pfizer for being the expert advisor in the advisory board before the development of the manuscript. None of the authors intend to unduly influence or promote any product through this publication. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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**References**

1. Zimmetbaum P: Atrial fibrillation. Ann Intern Med. 2017, 166:35-48. 10.7532/AITC201703070
2. Patel NJ, Atti V, Mitranu RD, Viles-Gonzalez JF, Goldberger JJ: Global rising trends of atrial fibrillation: a major public health concern. Heart. 2018, 104:1989-90. 10.1136/heartjnl-2018-313530
3. Freedman B, Hindricks G, Banerjee A, et al.: World Heart Federation Roadmap on Atrial Fibrillation - a 2020 update. Glob Heart. 2021, 16:10.5334/gbh.1023
4. Vora A, Kapoor A, Nair M, et al.: Clinical presentation, management, and outcomes in the Indian Heart Rhythm Society-Atrial Fibrillation (IHRSA-MA) registry. Indian Heart J. 2017, 69:43-7. 10.1016/j.ihj.2016.06.016
5. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY: Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med. 2010, 123:638-645.e4. 10.1016/j.amjmed.2009.11.025
6. Camm AJ, Kirchhof P, Lip GY, et al.: Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010, 31:2356-629. 10.1093/eurheartj/ehq278
7. Lin HJ, Wolf PA, Kelly-Hayes M, Reiber AS, Kase CS, Benjamin EJ, D'Agostino RB: Stroke severity in atrial fibrillation. The Framingham Study. Stroke. 1996, 27:1760-4. 10.1161/aha.1996.27.10.1760
8. Desevaniya P, Acharya T: Anticoagulation in atrial fibrillation: is the paradigm really shifting?. J Am Coll Cardiol. 2017, 69:786-8. 10.1016/j.jacc.2016.11.062
9. Reiffel JA: Time in the therapeutic range for patients taking warfarin in clinical trials: useful, but also misleading, misused, and overinterpreted. Circulation. 2017, 135:1475-7. 10.1161/CIRCULATIONAHA.116.026854
10. Oldgren J, Healey JS, Ezekowitz M, et al.: Variations in cause and management of atrial fibrillation in a prospective registry of 15,400 emergency department patients in 46 countries: the RE-LY Atrial Fibrillation Registry. Circulation. 2014, 129:1568-76. 10.1161/CIRCULATIONAHA.113.054571
11. January CT, Wann LS, Calkins H, et al.: 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2019, 74:104-52. 10.1016/j.jacc.2019.01.011
12. Hindricks G, Potpara T, Dugres N, et al.: 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS); the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021, 42:573-498. 10.1093/eurheartj/ehaa612
13. Steffen J, Collins R, Antz M, et al.: 2021 European Heart Rhythm Association Practical Guide on the use of non-vitamin k antagonist oral anticoagulants in patients with atrial fibrillation. Europace. 2021, 23:1612-76. 10.1093/europace/euab665
14. Lownes N, Neubeck L, Redfern J, Freedman SB: Screening to identify unknown atrial fibrillation. A systematic review. Thromb Haemost. 2015, 110:213-22. 10.1160/TH15-02-0165
15. Sandhu RK, Conen D, Tedrow UB, et al.: Predisposing factors associated with development of persistent compared with paroxysmal atrial fibrillation. J Am Heart Assoc. 2014, 3:10.1161/JAHA.113.000916
16. Brandes A, Smit MD, Nguyen BO, Riemstra M, Van Gelder IC: Risk factor management in atrial fibrillation. Am J Med. 2010, 123:638-645.e4. 10.1016/j.amjmed.2009.11.025
17. Gutierrez C, Blanchard DG: Diagnosis and treatment of atrial fibrillation. Am Fam Physician. 2016, 94:442-52.
18. CHA2DS2-VASc 1. to anticoagulate or not?. Accessed: January 31, 2020: https://www.escardio.org/static_file/Esocardio/Subspecialty/ER/HA/Documents/summit-2015/Lip%20CHA2DS2VA...-
19. HAS-BLED tool - what is the real risk of bleeding in anticoagulation?. (2012). https://www.acc.org/latest-in-cardiology/articles/2014/07/18/15/15/has-bled-tool-what-is-the-real-risk-of-bleeding-in-
20. Kirchhof P, Benussi S, Kotecha D, et al.: 2016 ESC Guidelines for the management of atrial fibrillation
developed in collaboration with EACTS. Eur Heart J. 2016, 37:2895-962. 10.1093/eurheartj/ehw210

21. Saraf K, Morris PD, Garg P, Sheridan P, Storey R: Non-vitamin K antagonist oral anticoagulants (NOACs): clinical evidence and therapeutic considerations. Postgrad Med J. 2014, 90:520-8. 10.1136/postgradmedj-2014-132665

22. Binymin KA, Nasher M, Patel D: Warfarin-induced deep vein thrombosis. Int Med Case Rep J. 2014, 7:125-5. 10.2147/IMCRJ.S62100

23. Haas S: New oral Xa and IIa inhibitors: updates on clinical trial results. J Thromb Thrombolysis. 2008, 25:52-60. 10.1007/s11239-007-0108-7

24. Mekaj YH, Mekaj AY, Ducu SB, Militari EI: 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, 11:967-77. 10.2147/TCRM.S84110

25. Ruff CT, Giugliano RP, Hoffman EB, et al.: Comparison of the effi cacy and safety of new oral anticoagulants with warfarin in patients with atrial fi brillation: a meta-analysis of randomised trials. Lancet. 2014, 383:955-62. 10.1016/S0140-6736(13)62543-0

26. Lip GY, Keshiahian A, Li X, et al.: Effectiveness and safety of oral anticoagulants among nonvalvular atrial fi brillation patients. Stroke. 2018, 49:2935-44. 10.1161/STROKEAHA.118.020232

27. Kundra A, Sardar P, Chatterjee S, Aronow WS, Owan T, Ryan JH: Minimizing the risk of bleeding with NOACs in the elderly. Drugs Aging. 2016, 33:491-500. 10.1007/s40266-016-0356-z

28. Capranzano P, Miccié E, D’Urso L, Privitera F, Tamburino C: Personalizing oral anticoagulant treatment in patients with atrial fi brillation. Expert Rev Cardiovasc Ther. 2015, 11:959-73. 10.1586/14770722.2015.818819

29. Kuhn-Thiel AM, Weiß C, Wehling M: Consensus validation of the FORTA (Fit For The Aged) list: a clinical tool for increasing the appropriateness of pharmacotherapy in the elderly. Drugs Aging. 2014, 31:131-40. 10.1007/s40266-013-0146-0

30. Pazzan F, Collins R, Gil VM, et al.: A structured literature review and international consensus validation of FORTA labels of oral anticoagulants for long-term treatment of atrial fi brillation in older patients (OAC-FORTA 2019). Drugs Aging. 2020, 37:539-48. 10.1007/s40266-020-00771-0

31. van Zyl M, Abdullah HM, Noseworthy PA, Siontis KC: Stroke prophylaxis in patients with atrial fi brillation and end-stage renal disease. J Clin Med. 2020, 9:10.3390/jcm9010123

32. Co AS, Fang MC, Udaltsouva N, Chang Y, Pomeranzki NK, Borowky L, Singer DE: Impact of proteinuria and glomerular fi ltration rate on risk of thromboembolism in atrial fi brillation: the anticoagulation and risk factors in atrial fi brillation (ATRIA) study. Circulation. 2009, 119:1563-9. 10.1161/CIRCULATIONAHA.108.816082

33. Alonso A, Lopez FL, Matsushita K, et al.: Chronic kidney disease is associated with the incidence of atrial fi brillation: the Atherosclerosis Risk in Communities (ARIC) study. Circulation. 2011, 123:2946-53. 10.1161/CIRCULATIONAHA.111.020992

34. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA: Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fi brillation and renal dysfunction. J Am Coll Cardiol. 2017, 69:2779-90. 10.1016/j.jacc.2017.05.060

35. Mendonca S, Gupta D, Valsa A, Tewari R: Warfarin related acute kidney injury: a case report. Indian J Nephrol. 2017, 27:78-80. 10.4103/0971-4406.177142

36. Eliquis (apixaban). (2014). https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/201555s006lbl.pdf

37. Shroff GR: NOAC dosing in atrial fi brillation and renal dysfunction: what measure are you using? J Am Coll Cardiol. 2017, 70:2735-4. 10.1016/j.jacc.2017.09.1091

38. Heiné GH, Brandenburg V, Schirmer SH: Oral anticoagulation in chronic kidney disease and atrial fi brillation. Dtsch Arztebl Int. 2018, 115:287-94. 10.3238/arztebl.2018.0287

39. Aursulesei V, Costache II: Anticoagulation in chronic kidney disease: from guidelines to clinical practice. Clin Cardiol. 2017, 40:2774-82. 10.1002/clc.23196

40. Nares® - highlights of prescribing information. (2018). Accessed: January 8, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022406e028bl.pdf

41. Qamar A, Vaduganathan M, Greenberger NJ, Giugliano RP: Oral anticoagulation in patients with liver disease. J Am Coll Cardiol. 2018, 71:2162-75. 10.1016/j.jacc.2018.05.023

42. Chang HY, Zhou M, Tang W, Alexander GC, Singh S: Risk of gastrointestinal bleeding associated with oral anticoagulants: population based retrospective cohort study. BMJ. 2015, 350:10.1136/bmj.h1585

43. De Caterina R, Lip GY: The non-vitamin K antagonist oral anticoagulants (NOACs) and extremes of body weight-a systematic literature review. Clin Res Cardiol. 2017, 106:S65-72. 10.1007/s00392-017-1102-5

44. Steffen J, Verhamme P, Potpara TS, et al.: The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fi brillation. Eur Heart J. 2018, 39:1350-95. 10.1093/eurheartj/ehy136

45. Chiang CE, Okumura K, Zhang S, et al.: 2017 consensus of the Asia Pacifi c Heart Rhythm Society on stroke prevention in atrial fi brillation. J Arrhythm. 2017, 33:345-67. 10.1016/j.joa.2017.05.004

46. Gerner HC, Aisenberg J, Ansell J, et al.: Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fi brillation: part 2. Eur Heart J. 2017, 38:860-8. 10.1093/eurheartj/ehw069

47. Lip GY, Banerjee A, Boerrig L, et al.: Antithrombotic therapy for atrial fi brillation: CHEST guideline and expert panel report. Chest. 2018, 154:1121-201. 10.1016/j.chest.2018.07.040

48. Lip GY: My approach to the use of NOACs for stroke prevention in patients with atrial fi brillation. Trends Cardiovasc Med. 2014, 24:263-6. 10.1016/j.tcm.2014.02.012

49. Verheugt F, Crager C: Oral anticoagulants for stroke prevention in atrial fi brillation: current status, special situations, and unmet needs. Lancet. 2015, 386:303-10. 10.1016/S0140-6736(15)60245-8

50. Hohnloser SH, Basic E, Nabauer M: Changes in oral anticoagulation therapy over one year in 51,000 atrial fi brillation patients at risk for stroke: a practice-derived study. Thromb Haemost. 2019, 119:882-93. 10.1055/s-0039-1685428