



REVIEW

# Expert Recommendations on the Usage of Non-vitamin K Antagonist Oral Anticoagulants (NOACs) from India: Current Perspective and Future Direction

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## ABSTRACT

Non-vitamin K antagonist oral anticoagulants (NOACs) are a new class of anticoagulant drugs used in the prevention and treatment of venous thromboembolism (VTE) and atrial fibrillation (AF). Anticoagulation requires the integration of the correct type and dose of oral anticoagulants based on patient characteristic, and therefore therapy needs to be individualized for each patient. Growing scientific evidence from studies on NOACs has led to a better understanding of their benefits and safety. A large amount of available data creates a necessity for

an adaptable practical document for the usage of NOACs in India. The current consensus, developed by experts from India, aims to give recommendations on various frequently raised clinical questions with regards to NOACs and its usage. This practical document provides a platform upon which future guidelines, policies, training, and education for the use of NOACs can be tailored.

**Keywords:** Anticoagulants; Venous thromboembolism; Atrial fibrillation; Rivaroxaban; Apixaban; Edoxaban

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### Key Summary Points

Despite the complexity of the prevention and management of venous thromboembolism (VTE) and non-valvular atrial fibrillation (NVAF), there are no specific guidelines in India and international guidelines are not standardized in the country.

Non-vitamin K antagonist oral anticoagulant (NOACs) have been approved as alternatives to warfarin and other vitamin K antagonists (VKA) for the prophylaxis of stroke and systemic embolic events (SEE) in patients with NVAF, and for treatment and prophylaxis of VTE.

NOACs significantly reduce stroke or systemic embolic events, hemorrhagic stroke, intracranial hemorrhage, and major bleeding in patients with VTE. Though both NOACs and VKAs can be used for the prevention of VTE, NOACs have a more significant relative reduction in major bleeding.

The dose and duration of NOAC therapy should be individualized after careful assessment of the treatment benefit against the risk of bleeding.

## EXPERT GROUP RECOMMENDATIONS

### Venous Thromboembolism

1. NOACs or VKAs can be used for the prevention of recurrent VTE.
2. In VTE, NOACs compared to VKA have a significant relative reduction in major bleeding.
3. The decision of a once-daily or twice-daily NOAC regimen in VTE should be based on

patient characteristics and clinical condition.

4. The duration of NOAC therapy should be individualized after careful assessment of the treatment benefit against the risk of bleeding. Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g., recent surgery, trauma, and immobilization) and longer durations should be based on permanent risk factors or idiopathic deep vein thrombosis (DVT)/pulmonary embolism (PE).
5. NOACs or other anticoagulants such as VKA and low molecular weight heparin (LMWH) can be used in chronic kidney disease (CKD) patients with VTE.
6. NOACs should be the first choice among currently available anticoagulants in elderly patients.
7. NOACs or LMWHs can be used in cancer patients with VTE.
  - a) Precaution for high risk of bleeding, as those with gastrointestinal and genitourinary cancer.

### Atrial Fibrillation (AF)

1. NOACs compared to warfarin significantly reduced stroke or systemic embolic events, hemorrhagic stroke, intracranial hemorrhage, and major bleeding in patients with VTE.
2. Once- or twice-daily NOAC regimen can be used in patients with atrial fibrillation (AF).
3. Duration of therapy in AF must be individualized after careful assessment of the treatment benefit against the risk of bleeding. For patients with AF of greater than 48 h or unknown duration undergoing elective electrical or pharmacologic cardioversion, it is recommended that therapeutic anticoagulation should be started for at least 3 weeks before cardioversion and should be continued for at least 4 weeks post successful cardioversion. Decisions about anticoagulation beyond 4 weeks should be made in accordance with risk-based

recommendations for long-term antithrombotic therapy and not based on successful cardioversion.

- 4 In AF patients eligible for NOACs, it is recommended to use a NOAC in preference to a VKA in combination with antiplatelet therapy.
- 5 In CKD patients, stage 1–3: NOACs are preferred. In CKD stage 4: NOACs or warfarin, the choice between will depend on the pharmacokinetics of the drugs and patient characteristics. In End-stage renal disease (ESRD): Warfarin remains the first-line treatment (to use or not to use anticoagulation is strictly individualized).
- 6 NOACs may be preferred in elderly patients, since they have a better overall risk–benefit profile compared with warfarin.

### Venous Thromboembolism or Atrial Fibrillation

- 1 Mild hepatic impairment: All NOACs could be considered without any dose adjustments.  
Moderate hepatic impairment: Dabigatran, apixaban, and edoxaban are viable options in patients with moderate hepatic impairment and do not require dose adjustments.  
Severe hepatic impairment: All NOACs are contraindicated. Warfarin is the only recommended anticoagulant in this patient population.
- 2 Any NOAC can be used in obese patients with body mass index (BMI)  $< 40 \text{ kg/m}^2$ . In patients with a BMI of  $40\text{--}50 \text{ kg/m}^2$ , warfarin should be used, but apixaban or edoxaban can be considered. In obese patients with a BMI  $> 50 \text{ kg/m}^2$ , warfarin should be used.
- 3 Factors to consider when choosing an oral anticoagulant include compliance, renal function, history of GI bleeding, concomitant medication, age, the need for aspirin, dosing, and cost. It is important to stratify the risk of stroke and hemorrhage for an individual patient before selecting OAC.
- 4 For re-starting NOAC post-procedure—restart 2 days after a high bleeding risk

procedure and restarted 1 day after a low/moderate bleeding risk procedure.

- 5 Reversal agents are indicated in patients with major bleed. Non-major/minor bleed—reversal agents not required, withholding the next NOAC doses is sufficient. The choice of NOAC should not be based on the availability of its respective reversal agents.
- 6 In case of a missed dose, the forgotten dose can be taken up to 6 h or up to 12 h after the scheduled intake for a BD or OD regimen, respectively. If this is not possible, the dose should be skipped and the next scheduled dose taken. In case of a double dose on a BD regimen, the next planned dose can be skipped and restarted BD after 24 h while in OD dosing, the normal regimen can be continued. In case of overdose, dabigatran can be removed via dialysis. Rivaroxaban and apixaban are not dialyzable, hence use reversal agents.

## INTRODUCTION

Venous thromboembolism (VTE) and atrial fibrillation (AF) implicate a high burden of mortality and morbidity. In India, about 2,31,132 VTE events occur annually and 53.6% of the hospitalized Indian patients are at an increased risk of VTE. The age group commonly affected with VTE is 41–60 years [1]. General surgery and orthopedics department observe a higher incidence of VTE [2]. The burden of AF in India is high due to the high prevalence of the associated risk factors, especially hypertension and diabetes mellitus. Prophylaxis of AF and VTE is a cost-effective measure, as costs of management of deep vein thrombosis (DVT) and pulmonary embolism (PE) are very high [3]. The rising incidence of VTE across India may be attributable to the aging population, dietary changes, and increasing incidence of obesity and diabetes. AF, an important risk factor for cardioembolic stroke, is the most common sustained cardiac arrhythmia [4, 5]. In India, valvular AF patients comprise not just those with mechanical heart valves but also those

with rheumatic mitral stenosis. There has been a steady increase in AF incidence over the last two decades. This trend is likely to continue over the next few decades with an aging population and higher occurrence of the associated risk factors, including cardiac diseases. Despite major advances in its management, AF remains a significant cause of cardiovascular morbidity and mortality, especially that arising from stroke and heart failure (HF) [6].

Non-vitamin K antagonist oral anticoagulant (NOACs) have been approved as alternatives to warfarin and other vitamin K antagonists (VKA) for the prophylaxis of stroke and systemic embolic events (SEE) in patients with non-valvular atrial fibrillation (NVAf), treatment, and prophylaxis of VTE. The NOACs fall into two major categories: direct thrombin (factor IIa) inhibitors (dabigatran) and direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban). Several clinical trials have proved these agents as safe and efficacious [3]. In addition, they have added advantages such as rapid onset and termination of the action, predictable anticoagulant effect such that routine laboratory monitoring is not required [5–9]. For patients with DVT and/or PE, the American Society of Hematology (ASH) guideline 2020 panel suggests using NOACs over VKAs (conditional recommendation) [10]. Atrial fibrillation increases mortality and many cardiovascular and cerebrovascular events, including HF and acute coronary syndrome (ACS) [11]. NOACs significantly reduce stroke or systemic embolic events by 19% compared with warfarin [12].

Warfarin and other VKAs antagonists have several limitations that make it difficult to use in clinical practice. Warfarin, the conventional oral anticoagulant has several limitations and challenges, such as resistance due to VKORC1 genetic polymorphisms, a narrow therapeutic window with international normalized ratio (INR) range 2–3, routine coagulation monitoring, unpredictable pharmacokinetics, slow-onset/offset of action, increased risk of bleeding including intracranial hemorrhage, dose adjustment, dietary restrictions, drug interactions, high coefficient of inter-lab variation in INR estimation; INR is not reflective of monthly or long-term control [13, 14].

## The Extent of the Problem

Patients who develop a VTE are more likely to have an extended hospital stay with additional economic costs, mainly attributable to the extended length of stay. Indirect costs, such as loss of productivity by the patient and an increased burden on their careers, further add to the economic cost of thromboembolism to healthcare systems. The incidence of VTE may be influenced by rising rates of urbanization, reduced medical adherence, hypertension, diabetes, obesity, knee replacement, and other elective surgeries [1–3].

## Need for Consensus

The prevention of VTE is complex and requires the integration of a correct choice and dosing of an oral anticoagulant (OAC). Between 2009 and 2013, four different compounds were compared with conventional therapy for the treatment of acute VTE and NVAf. In total, 27,023 patients were enrolled in six phase 3 randomized controlled trials. Clinicians will need to choose between these new anticoagulants and standard treatment, and they will need clinically relevant information as to whether these agents are indeed suited for all of their patients with VTE. Furthermore, stoppage and restarting of NOACs are critical before and after surgery. However, there are no specific guidelines in India and international guidelines are not standardized in the country. Hence, there is a need for an adaptable practical document for oral anticoagulants for VTE and AF in India. To aid the clinician in dealing with the overwhelming amount of information, we present a draft recommendation on various frequently raised clinical questions.

## Methods

The primary target audience for this practical document is surgeons and nurses. The recommendations are also intended to be used by policy-makers as the basis for developing national and local anticoagulation protocols and policies and supporting staff education and

training. A diverse group of practitioners was therefore chosen for the expert panel to represent a wide and holistic view on NOAC for prevention and treatment of AF and VTE. The main aim of this practical document is to give recommendations for better patient outcomes and services in all types of hospitals. Therefore, the experts were asked to deliberate on NOACs for AF and VTE from an Indian perspective. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## NOACS IN VTE

### Why are NOACs Chosen over VKAs for the Treatment of VTE?

In the last 4 years, six phase 3 trials including a total of 27,023 patients with venous thromboembolism (VTE) compared a NOAC with VKA. Recurrent VTE occurred in 2.0% of NOAC recipients compared with 2.2% in VKA recipients (relative risk [RR] 0.90). Treatment with a NOAC significantly reduced the risk of major bleeding (RR 0.61). In parallel, intracranial bleeding, fatal bleeding, and clinically relevant non-major bleeding occurred significantly less in NOAC recipients. Factor Xa inhibitors (NOACs) were as effective as VKAs in the prevention of recurrent VTE, with a significant relative reduction of 44% in major bleeding. NOACs are safe and effective in key clinical groups such as patients with PE, DVT, a body-weight  $\geq 100$  kg, moderate renal insufficiency, an age  $\geq 75$  years, and cancer [7].

The ASH 2020 guidelines recommend using NOACs over VKAs in patients with DVT and/or PE. The use of a NOAC instead of a VKA for patients with VTE does not impact mortality (RR = 0.99; or the risk of PE RR = 0.97). The use of a NOAC was associated with a reduction in the risk of major bleeding (RR = 0.63). Patients with a high bleeding risk may benefit from a NOAC instead of a VKA in terms of fewer bleeding events per 1000 patients [10].

### Risk Assessment of VTE Patients About to Start Anticoagulation Treatment

Several scoring systems such as the Vienna prediction model (VPM), DASH score, and the HERDOO2 scoring system are used to predict the risk of recurrence of VTE after a first unprovoked episode. The Vienna prediction model calculates the cumulative recurrence risk (CRR) of VTE using different parameters like sex, location of the first VTE event, and d-dimer level after cessation of anticoagulation [15]. The VPM could aid clinicians in estimating this risk, thus help in deciding the dose and duration of the prescribed NOAC. The updated VPM integrates patient's parameters and serial d-dimer measurements allowing prediction of recurrent VTE from multiple random times after discontinuation of oral anticoagulation [16]. The initial treatment of VTE is based on patient characteristics (Fig. 1).

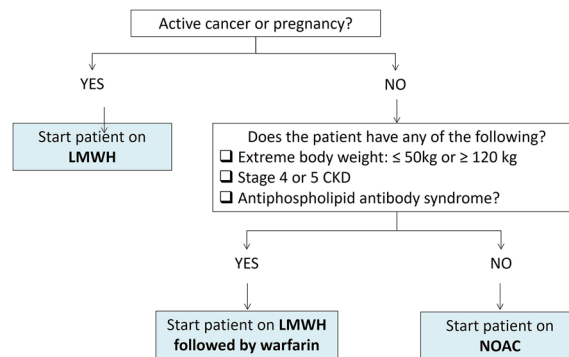
### NOAC Dose for the Treatment and Prevention of VTE

Dosing of NOACs in patients with VTE.

Table 1 describes the dosing regimen of NOACs for initial treatment and secondary prevention of VTE [18].

### Once- or Twice-Daily NOAC Therapy in VTE

A meta-analysis of 12 RCTs and 10,716 patients, compared different regimens of all NOACs,



**Fig. 1** Initial treatment of VTE [17]. CKD chronic kidney disease, LMWH low molecular weight heparin

**Table 1** Dosing of NOACs in patients with VTE [18]

NOAC	VTE initial treatment	VTE secondary prevention after initial therapy
Apixaban	10 mg orally twice daily for the first 7 days of therapy followed by 5 mg orally twice daily	After $\geq$ 6 months of initial therapy, either 5 mg orally twice daily or 2.5 mg orally twice daily can be considered
Dabigatran	150 mg orally twice daily when preceded by 5–10 days of parenteral AC	150 mg orally twice daily
Edoxaban	60 mg orally once daily when preceded by at least 5–10 days of parenteral AC	60 mg orally once daily
Rivaroxaban	15 mg orally twice daily with food for the first 21 days followed by 20 mg daily with food	After $\geq$ 6 months of initial therapy, either 20 mg orally daily with food or 10 mg orally daily with or without food can be considered

AC anticoagulant

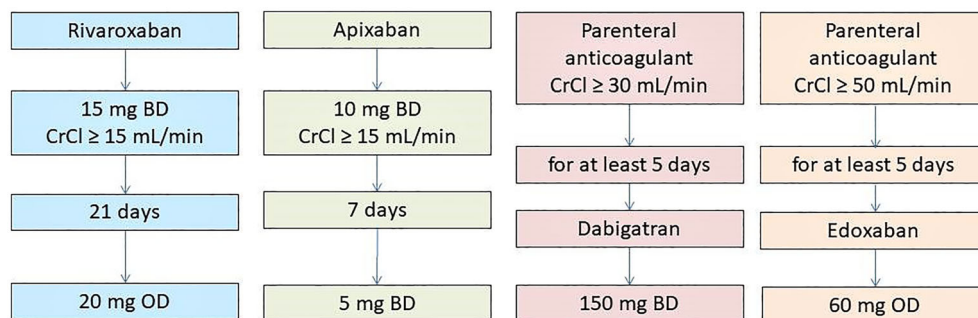
concluded that there is no difference in efficacy and safety between the once daily (OD) and twice daily (BD) regimens of NOACs in patients with VTE, NVAf, ACS and major orthopedic surgery (MOS) [19]. Rivaroxaban OD regimens were studied in various VTE trials such as RECORD and EINSTEIN-EXT. Most studies suggest that once-daily dosing may be suitable for most rivaroxaban indications including VTE and AF. The elimination half-life ( $t_{1/2}$ ) of rivaroxaban is prolonged in elderly patients, thus rivaroxaban OD may be suitable for geriatric patients. Thus, a “one-size-fits-all” approach regarding frequency may not be the right choice for patients. Thus, both patient and drug characteristics must be considered [20].

The anticoagulant effects of edoxaban are rapid in onset ( $T_{max}$  1–2 h) and sustains for up to 24 h [21]. The Hokusai VTE study demonstrated edoxaban 60 mg orally once daily to be non-inferior to warfarin for VTE recurrence [HR 0.89] [22]. The efficacy of twice daily dose of apixaban was observed in AMPLIFY and AMPLIFY-EXT study [23, 24]. The AMPLIFY study patients received apixaban 10 mg twice daily orally for 7 days followed by apixaban 5 mg twice daily orally for 6 months. AMPLIFY-EXT study patients received apixaban 2.5 mg orally twice daily or 5 mg orally twice daily for 12 months. Both studies demonstrated non-inferiority of apixaban to enoxaparin/warfarin and superiority to placebo for recurrent symptomatic VTE.

### Duration of NOAC Therapy in VTE Patients

Approved dose and duration regimens of NOACs for the treatment of VTE is mentioned in Fig. 2.

For rivaroxaban, a reduction in the dose from 20 to 15 mg OD should be considered if the patient’s assessed risk of bleeding outweighs the risk of recurrent DVT/PE. Rivaroxaban should be used with caution in patients with creatinine clearance (CrCl) of 15–29 ml/min and is not recommended in patients with CrCl < 15 ml/min. For apixaban, the prevention of recurrent DVT or PE following completion of 6 months of treatment for DVT or PE, 2.5 mg twice daily (BD) is recommended. Apixaban should be used with caution in patients with CrCl 15–29 ml/min and is not recommended in patients with CrCl < 15 ml/min. For dabigatran, the dose should be selected based on individual assessment of the thromboembolic and bleeding risks: age 75–80 years; moderate renal impairment; gastritis, esophagitis, or gastroesophageal reflux, and increased risk of bleeding. Dabigatran is contraindicated in patients with severe renal impairment (CrCl < 30 ml/min). For edoxaban 30 mg, OD is recommended in patients with one or more of the following clinical factors: moderate or severe renal impairment (CrCl 15–50 ml/min), low body weight (< 60 kg), or concomitant use of



**Fig. 2** Dose regimens of the NOACs (based on the EU labels) for the treatment of VTE [25]. *OD* once-daily, *BD* twice-daily, *CrCl* creatinine clearance

the following P-gp inhibitors: cyclosporin, dronedaron, erythromycin, or ketoconazole [25].

### Special Population

#### **Chronic Kidney Disease (CKD) and VTE**

NOACs and other anticoagulants including VKA and LMWH showed no statistical difference in preventing recurrent VTEs among CKD patients. NOACs had a significantly lower risk of major and non-major clinically relevant bleeding irrespective of the level of renal impairment compared to VKAs [18].

The Italian Society of Nephrology suggests that NOAC have at least similar efficacy and safety profiles as VKA in patients with CKD stage G2 (CrCl 60–89 ml/min) to G3b (30–44 ml/min), while in patients with CKD G4 (15–29 ml/min) to G5 (< 15 ml/min), also on long-term dialysis, NOAC should be used with caution. Careful monitoring of renal function in patients taking NOAC is recommended to avoid the risk of overdosing [26].

#### **The Elderly and Frail with VTE**

The incidence of VTE and VTE-related morbidity and mortality increases with advancing age. Thus, in elderly patients, NOACs are not only associated with a lower risk of bleeding but they even appear to be more efficacious than vitamin K antagonists in preventing recurrent VTE during the acute treatment period [15]. Using NOAC in elderly patients has been associated with a superior efficacy profile and no increase in bleeding events, compared to conventional

anticoagulation. Thus, NOACs should be the first choice among currently available anticoagulants in elderly patients [27]. In non-AF trials, NOACs also had a significantly lower risk of VTE or VTE-related death than conventional therapy in elderly adults [28]. In the absence of conclusive data, standard dose of NOAC is initially prescribed to elderly patients with acute VTE. But, since lower dose of apixaban and rivaroxaban are effective and have a lower risk of bleeding in extending treatment of VTE, it is suggestive to consider these lower doses in elderly requiring long-term anticoagulation for preventing recurrent VTE [29].

recurrent VTE.

#### **Cancer and VTE**

Patients with cancer-associated venous thrombosis (CAT) have an elevated risk of both recurrent VTE, due to their prothrombotic status, and bleeding complications, due to the cancer lesion, chemotherapy, and related thrombocytopenia. In patients with cancer, results from recent randomized trials have reported that the efficacy and safety profile of NOACs does not differ from those of LMWHs. Thus, NOACs are a valid option for the treatment of VTE in these patients. However, for the management of cancer patients at high risk of bleeding, as those with gastrointestinal and genitourinary cancer who require carefully monitoring, LMWH should be the treatment of choice [18].

Major guidelines recommend the use of LMWH for the treatment of cancer-associated VTE and have recently added the use of

**Table 2** Clinical studies of cancer-associated VTE [31]

Landmark trial	N	Intervention (dose and duration)	Results		
SELECT-D	203	Dalteparin (200 IU/kg daily during month 1, then 150 IU/kg daily for months 2–6)	Outcome	R	D
			Recurrent VTE	8	18
		Or Rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg once daily for a total of 6 months)	6-month cumulative VTE recurrence rate	4% (HR 0.43)	11%
			6-month cumulative rate of major bleeding	6% (HR 1.83)	4%
HOKUSAI-VTE cancer	1046	Edoxaban group: LMWH for at least 5 days followed by oral edoxaban at a dose of 60 mg once daily	Outcome	E	D
			Composite of recurrent VTE	12.8% (HR 0.97, $p = 0.006$ for non-inferiority)	13.5%
		Or Dalteparin group: SC dalteparin at a dose of 200 IU/kg of body weight once daily for 1 month followed by dalteparin at a dose of 150 IU/kg once daily	Recurrent VTE	7.9%	11.3%
			Major bleeding	6.9%	4%
Treatment duration—at least 6 months and up to 12 months					
CARAVAGGIO	1155	Apixaban oral 10 mg BID for the first week, followed by 5 mg BID	Outcome	A	D
			Recurrent VTE	5.6%	7.9%
		Or Dalteparin SC 200 IU/kg QD for the first month, and then 150 IU/kg QD (up to 18,000 IU and according to the platelet count)	Major bleeding	3.8%	4%
			Treatment duration—6 months		

edoxaban or rivaroxaban. In the Caravaggio trial, oral apixaban (10 mg BD for the first 7 days, followed by 5 mg BD) was compared to subcutaneous dalteparin (200 IU/kg OD for the first month, followed by 150 IU/kg OD) for the treatment of cancer-associated VTE. Apixaban was non-inferior to dalteparin in terms of recurrent VTE (5.6 vs. 7.9%,  $p < 0.001$  for non-inferiority), without an increased risk of major

bleeding (3.8 vs. 4.0%,  $p = 0.60$ ) [30]. Results of NOAC in cancer-associated VTE trials are mentioned in Table 2.

The SELECT D trial is multicenter, randomized, open-label, pilot trial, evaluating rivaroxaban vs. dalteparin. The study enrolled patients with active cancer who had symptomatic PE, incidental PE, or symptomatic lower-extremity proximal DVT. Rivaroxaban compared with



dalteparin was associated with relatively low VTE recurrence (4 vs. 11%) but higher CRNMB (6–13 vs. 4%) in cancer patients [32]. The HOKUSAI VTE-Cancer study is an open-label, noninferiority trial that demonstrated noninferiority of oral edoxaban to subcutaneous dalteparin with respect to the composite outcome of recurrent venous thromboembolism or major bleeding. Patients with cancer who had acute symptomatic or incidental VTE were enrolled. The rate of recurrent venous thromboembolism was lower (7.9 vs. 11.3%) but the rate of major bleeding was higher with edoxaban (6.9%) than with dalteparin (4%) [33]. The CARAVAGGIO trial is a multinational, randomized, controlled, open-label, non-inferiority trial evaluating apixaban vs. dalteparin for the prevention of recurrent VTE in oncologic outpatients. Enrolled patients had symptomatic or incidentally detected proximal lower limb DVT or PE. Apixaban resulted non-inferior to dalteparin for preventing VTE (5.6 vs. 7.9%,  $p < 0.001$  for non-inferiority) without increasing the risk of major bleeding (3.8 vs. 4%,  $p = 0.60$ ) in patients with cancer [24].

A meta-analysis showed that anticoagulant therapy with NOACs (apixaban, edoxaban, rivaroxaban, or dabigatran) may be more effective than traditional anticoagulants (VKA, LMWH, dalteparin, or enoxaparin) to prevent recurrent VTE (RR 0.60,  $p < 0.00001$ ) in patients with CAT, while the bleeding risk was similar in both groups (RR 0.95,  $p = 0.79$ ). Thus, NOACs may be more effective than traditional anticoagulants in preventing recurrent VTE in cancer patients, with no significant difference in safety. Hence, NOACs can be used as the first-line therapy for secondary prevention of CAT in most cancer patients [34].

The American Society of Clinical Oncology (ASCO) updated guidelines recommends rivaroxaban, edoxaban and LMWH as the first-choice options for VTE treatment. However, due to the observed gastrointestinal bleeding risk, NOACs use should be carefully evaluated in patients with gastric cancer. Before starting NOACs, potential drug–drug interactions (DDIs) and avoid their administration with chemotherapy drugs that strongly induce or

inhibit P-glycoprotein (P-gp) or CYP3A4 pathways [31].

### Guideline Recommendations

New CHEST Guidelines 2021 are mentioned in Table 3 [35].

## NOACS IN AF

### Why are NOACs Chosen over VKAs for the Treatment of AF?

Meta-analysis of RE-LY (dabigatran), ROCKET-AF (rivaroxaban), and ARISTOTLE (apixaban) included 42,411 participants with AF that received NOAC had significantly reduced stroke or systemic embolic events by 19% compared with warfarin (RR 0.81,  $p < 0.0001$ ), relative risk reduction (RRR) in hemorrhagic stroke by 51% (RR 0.81,  $p < 0.0001$ ) and reduction in intracranial hemorrhage by 52% (RR 0.48,  $p < 0.0001$ ). Furthermore, NOACs reduced major bleeding by a RRR of 14%. Low-dose NOAC had similar overall reductions in stroke or systemic embolic events compared to warfarin (1.03,  $p = 0.74$ ), and a more favorable bleeding profile (0.65,  $p = 0.05$ ), but significantly more ischemic strokes (1.28,  $p = 0.045$ ). The low-dose NOAC showed a significant reduction in all-cause mortality, similar to the higher-dose regimens [12]. The meta-analysis concluded that NOAC had a favorable risk–benefit profile, compared to warfarin. NOACs significantly reduced stroke, intracranial hemorrhage, and mortality. NOACs had a similar major bleeding, but increased gastrointestinal bleeding, compared to warfarin.

The Italian study showed that the differences between NOAC and VKA were much less when patients treated with VKA were regularly followed by the anticoagulation clinics. These clinics markedly improved management of VTE. Firstly, possible periods of under-anticoagulation were avoided and secondly improving the bridging with a parenteral anticoagulant especially during the first months of treatment was done [36, 37].

**Table 3** Recommendations from updated 2021 CHEST Guidelines for VTE [35]

Indication	Recommendation	Strength of recommendation
Cancer-associated VTE	DOACs should be used for the treatment phase of therapy*	Strong
VTE and antiphospholipid syndrome	Warfarin (target INR 2.5) is recommended over DOAC therapy during the treatment phase for VTE	Weak
Treatment-phase anticoagulants	DOACs are recommended over warfarin	Strong
Extended-phase therapy (beyond 3 months) for VTE	Extended anticoagulation should be offered to patients with unprovoked VTE <sup>#</sup>	Strong
	DOAC (low-dose apixaban or rivaroxaban) is recommended over full doses of these agents	Weak
	Aspirin is recommended for patients who are stopping anticoagulation	

\*For patients with luminal gastrointestinal malignancies, apixaban or low molecular weight heparin is preferred to reduce bleeding risk

<sup>#</sup>No major or minor transient risk factors. Risk for recurrent VTE, risk for bleeding, and patients' values and preferences should be considered in decisions about extended anticoagulation therapy

### Risk Assessment of AF Patients About to Start Anticoagulation Treatment

Thromboprophylaxis consists of stroke risk assessment and assessing bleeding risk. The 2012 focused update to the European Society of Cardiology (ESC) guidelines recommends stroke risk assessment using the CHA<sub>2</sub>DS<sub>2</sub>-VASc score. The HAS-BLED score is the recommended score in the ESC and Canadian guidelines for this purpose. HAS-BLED has been well validated in the past [38]. The assessment of the risk of anticoagulation in patients with AF involves the use of the CHA<sub>2</sub>DS<sub>2</sub>VASc, HAS-BLED, and SAMeTT<sub>2</sub>R scores to evaluate stroke risk, bleeding risk, and likelihood of successful warfarin therapy, respectively. NOACs may be considered where the SAMeTT<sub>2</sub>R score predicts poor control of anticoagulation with warfarin (Fig. 3).

Individual assessment of stroke risk and risk of bleeding with drug is the first step of deciding about appropriate stroke thromboprophylaxis. Use of risk assessment tools such as CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED can help doctors choose antithrombotic strategy. The validated

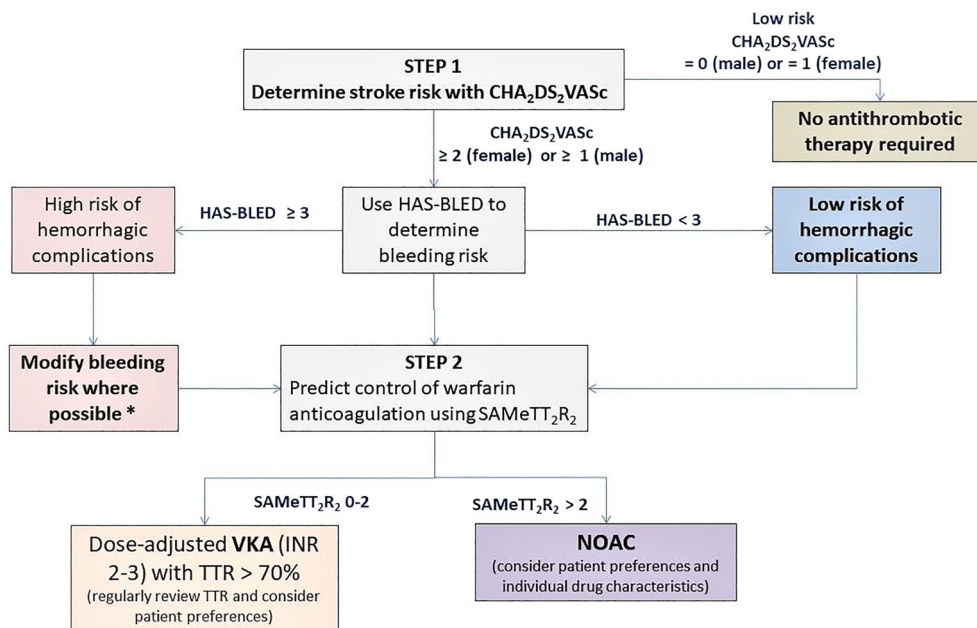
HAS-BLED allows the clinician to identify bleeding risk factors and to correct those that are modifiable [28]. HAS-BLED is more user friendly and is made up of clinical information that is routinely available before therapy is initiated [39]. Modified mCHA<sub>2</sub>DS<sub>2</sub>-VASc is a validated tool for stroke risk stratification [40].

### NOAC Dose for the Treatment of AF

Table 4 shows the dose of NOACs in AF [42].

### Once- or Twice-Daily NOAC Therapy in AF

A meta-analysis of six RCTs concluded that in Asian patients with AF, NOACs, regardless of dosing regimens, have a similar feature of preserved efficacy with improved safety compared with warfarin. There was no effect modification by dosing regimens in the risk of stroke or systemic embolism across ethnicities (all interaction  $p > 0.05$ ) [43]. All NOACS (without differences between regimens) showed a 10% reduction in all-cause mortality when compared with warfarin, seen in a fixed-effects meta-analysis [44].



**Fig. 3** Selection of stroke-prevention therapies in patients with non-valvular atrial fibrillation (NVAF) and risk factors based on the CHA2DS2-VASc score [41]. \*Uncontrolled hypertension, labile INRs, concomitant aspirin/NSAID use, alcohol excess. *VKA* vitamin K antagonist, *INR* international normalized ratio, *NSAID* non-steroidal anti-inflammatory drug, *OAC* oral

anticoagulant, *TTR* time in therapeutic range. Antiplatelet therapy with aspirin-clopidogrel or—less effectively— aspirin monotherapy (consider only in patients who are unwilling or unable to take any form of OAC whether VKA or NOAC)

In a multi-center, cross-sectional study, 2214 subjects with NVAF that took NOAC (once or twice daily) for 3 months showed that though twice-daily dosing of NOACs was associated with decreased adherence in patients, it was not an independent risk factor for bleeding complications [45]. A missed dose can be detrimental for patients, especially if the dose missed is of an oral anticoagulant. NOACs are usually prescribed for a long time, thus simple dosing schedules such as once-daily dosing may benefit patients. Medication adherence to NOACs is crucial to maintain an optimum level of efficacy and safety since compliance and adherence significantly affect outcomes in VTE and AF. Once-daily dosing has the potential to improve rates of stroke prevention in patients with AF [46]. A recently published meta-analysis does not observe a global difference of efficacy and safety between BD and OD regimens of NOACs in MOS, NVAF, VTE, and ACS [19].

Rivaroxaban administered once daily would improve medication adherence and patient outcomes, thus leading to long-term benefits in patients with non-valvular AF at risk of stroke [47]. The phase III study, ROCKET-AF validated Rivaroxaban 20 mg OD (CrCl ≥ 50 ml/min) and 15 mg OD (CrCl 30–49 ml/min) in patients with AF had similar efficacy [25]. Bleeding rates of twice-daily Edoxaban were higher than once-daily groups. Few real-world and retrospective studies observed that patients on once-daily dosing regimen had better adherence and persistence to therapy [48]. In both standard and reduced-dose regimens, edoxaban showed comparable effectiveness and safety compared to rivaroxaban in Korean patients with NVAF. Among four available NOACs, rivaroxaban and edoxaban have the advantage of once-daily administration, allowing convenience and lower pill burden [49].

**Table 4** Dose of NOACs in AF [26]

Parameter	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Standard dose	150 mg twice daily	20 mg once daily	5 mg twice daily	60 mg once daily
Lower dose	110 mg twice daily			
Reduced dose		15 mg once daily	2.5 mg twice daily	30 mg once daily
Dose-reduction-criteria	Dabigatran 110 mg b.i.d. in patients with: Age $\geq$ 80 years Concomitant use of verapamil, or Increased bleeding risk	CrCl 15–49 ml/min	At least 2 or 3 criteria: Age $\geq$ 80 years Body weight $\leq$ 60 kg, or Serum creatinine $\geq$ 1.5 mg/dl	If any of the following CrCl 15–50 ml/min Body weight $\leq$ 60 kg Concomitant use of dronedarone, cyclosporine, erythromycin, or ketoconazole

CrCl creatinine clearance

### Duration of NOAC Therapy in AF Patients

When contemplating the usage and duration of combination antithrombotic therapy in AF patients who have had an ACS or who are undergoing percutaneous coronary intervention (PCI), the risks of ischemic stroke/systemic embolism, coronary ischemia episodes, and antithrombotic treatment-related bleeding must be carefully considered. Overall, when compared to triple therapy, dual antithrombotic therapy with an OAC (preferably NOAC) and a P2Y12 inhibitor (preferably clopidogrel) is associated with significantly less major bleeding including intracranial hemorrhage (ICH). However, existing evidence suggests that in some AF patients who have recently had an ACS or are having PCI, at least a short course of triple therapy ( $\leq$  1 week) would be desirable in such patients, especially in those at increased risk of ischemic events (Fig. 4) [42].

### Secondary Stroke Prevention in AF Patients After Acute Ischemic Stroke

The 2020 European Society of Cardiology (ESC) guidelines recommend long-term secondary prevention of stroke using oral anticoagulant in

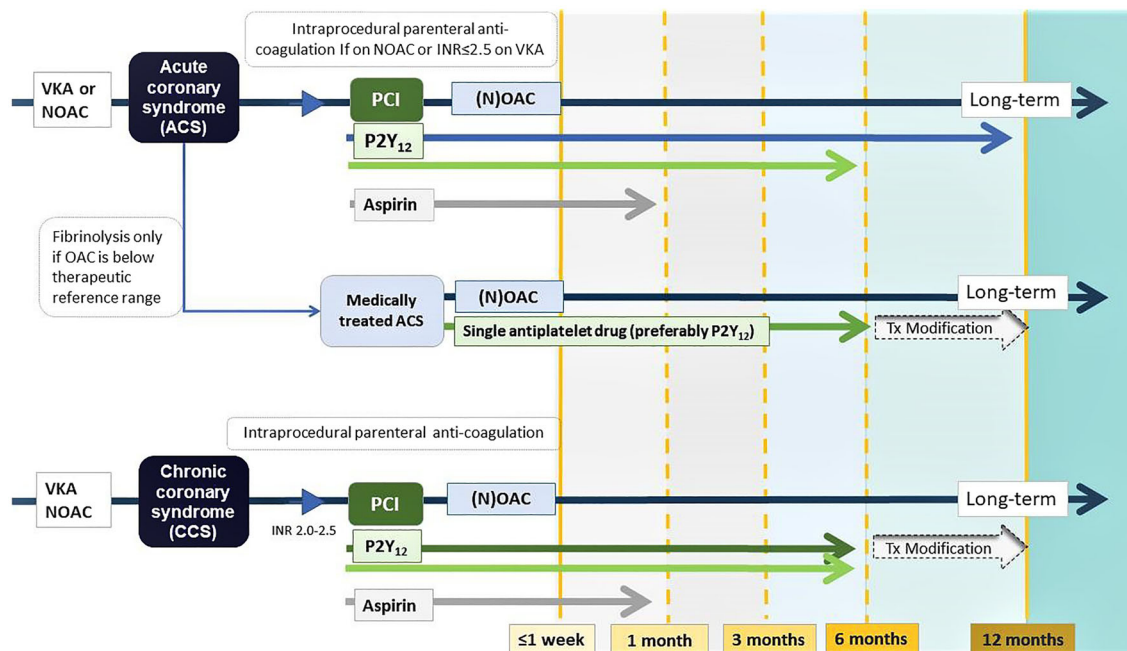
patients with AF and an ischemic stroke or transient ischemic attack (TIA), if there is no strict contraindication to OAC use, with a preference for NOACs over VKAs in NOAC-eligible patients [42].

### Dual Antiplatelet Therapy (DAPT)

Contemporary PCI involves the placement of a stent in vast majority of cases. This necessitates pharmacotherapy with dual antiplatelet therapy (DAPT) following stent implantation (Fig. 5; Table 5).

The number of patients undergoing PCI who mandate additional oral anticoagulant therapy has been increasing. It should be noted that the addition of a NOAC increases the likelihood of bleeding while on antiplatelet therapy. The overall risks and benefits for each patient undergoing PCI on NOACs must be assessed and therapy individualized to ensure optimal therapy for each unique clinical situation.

Both pivotal trials (PIONEER AF-PCI trial for rivaroxaban and RE-DUAL trial for dabigatran) reported significantly lower bleeding with the dual antithrombotic regimen compared to triple therapy. However, previous studies showed that triple therapy had a higher risk of bleeding



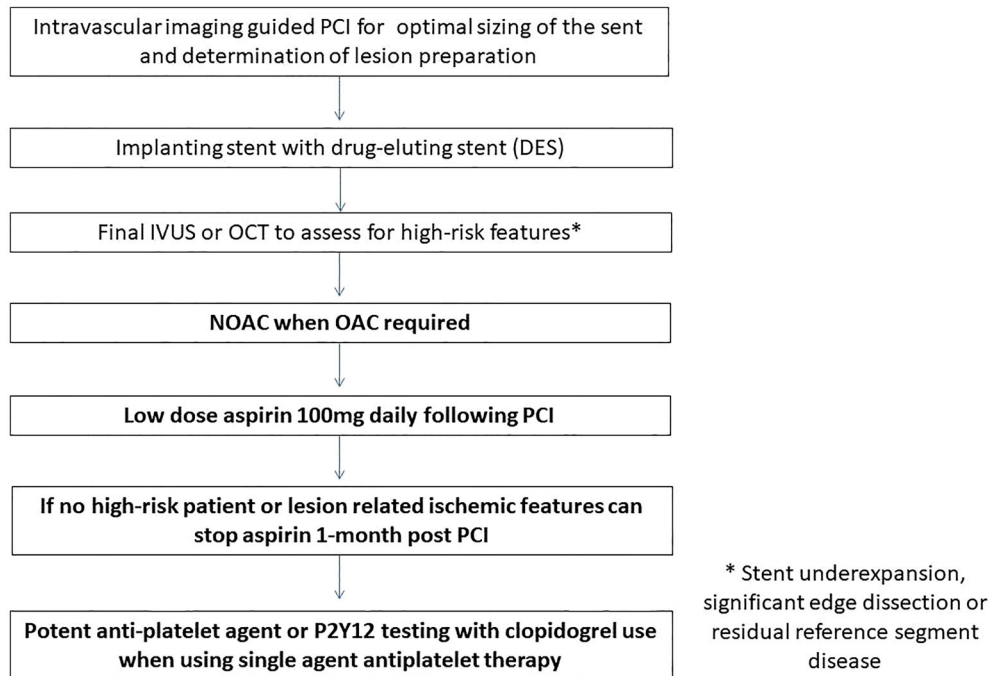
**Fig. 4** Post-procedural management of patients with AF and ACS/PCI [42]. *Full-outlined arrows*—default strategy; *dashed arrows*—treatment modifications. ACS acute coronary syndromes, ASA acetylsalicylic acid, CAD coronary artery disease, CCS chronic coronary syndromes, CKD chronic kidney disease, DAPT dual antithrombotic therapy, eGFR estimated glomerular filtration rate, ICH intracranial hemorrhage, INR international normalized ratio, LMWH low molecular weight heparin, MI

myocardial infarction, NOAC non-vitamin K antagonist oral anticoagulant, NSAID non-steroidal anti-inflammatory drug, OAC oral anticoagulant, PAD peripheral artery disease, PCI percutaneous coronary intervention, PPI proton-pump inhibitor, STEMI ST-segment elevation myocardial infarction, UFH unfractionated heparin, VKA vitamin K antagonist

[51]. A recent Danish study showed that AF patients on triple therapy experienced a higher rate of bleeding in comparison with dual therapy or monotherapy [52]. Furthermore, the 2020 ACC expert consensus does not recommend triple therapy for most patients due to increased bleeding risk [53]. The PIONEER AF-PCI trial included 2124 subjects with non-valvular AF treated with PCI. Patients were randomized to receive either low-dose rivaroxaban (15 mg OD) plus P2Y<sub>12</sub> inhibitor (group 1) or very low dose rivaroxaban (2.5 mg BD) plus DAPT (group 2), or standard therapy with a dose-adjusted vitamin K antagonist (OD) plus DAPT (group 3). The rates of clinically significant bleeding were lower in the two groups receiving rivaroxaban (15 mg once daily or 2.5 mg twice daily) than in the group receiving standard therapy (16.8% in group 1, 18.0% in

group 2, and 26.7% in group 3;  $p < 0.001$ ). In participants with atrial fibrillation undergoing PCI with the placement of stents, the administration of either low-dose rivaroxaban plus a P2Y<sub>12</sub> inhibitor for 12 months or very low dose rivaroxaban plus DAPT for 1, 6, or 12 months was associated with a lower rate of clinically significant bleeding than was standard therapy with a vitamin K antagonist plus DAPT for 1, 6, or 12 months [54].

In the RE-DUAL trial with 2725 subjects, patients were randomized to receive either dabigatran 110 mg or 150 mg with P2Y<sub>12</sub> inhibitor, or warfarin with P2Y<sub>12</sub> inhibitor and aspirin. In patients with AF who had undergone PCI, the benefits of both dabigatran doses (110 and 150 mg) dual therapy were comparable to warfarin triple therapy for the composite endpoint of death, myocardial infarction, stroke,



**Fig. 5** Stepwise approach to initiate NOAC while on DAPT [50]. \*Stent under-expansion, significant edge dissection or residual reference segment disease. *DAPT* dual antiplatelet therapy, *DES* drug-eluting stent, *IVUS*

intravascular ultrasound, *NOAC* novel oral anticoagulant, *OAC* oral anticoagulant, *OCT* optical coherence tomography, *PCI* percutaneous coronary intervention

**Table 5** Recommendation by 2020 ESC guidelines for DAPT [42]

Recommendation	Class of recommendation	Level of evidence
In AF patients eligible for NOACs, it is recommended to use a NOAC in preference to a VKA in combination with antiplatelet therapy	I	A
In patients at high bleeding risk (HAS-BLED $\geq 3$ ), rivaroxaban 15 mg OD should be considered in preference to rivaroxaban 20 mg OD for the duration of concomitant single or DAPT to mitigate bleeding risk	IIa	B
In patients at high bleeding risk (HAS-BLED $\geq 3$ ), dabigatran 110 mg b.i.d. should be considered in preference to dabigatran 150 mg b.i.d. for the duration of concomitant single or DAPT to mitigate bleeding risk	IIa	B

systemic embolism, or unplanned revascularization, with minor variations across all four subgroups (all interactions  $p$  values  $> 0.10$ ) [55]. DAPT is associated with reduced ischemic events including stent thrombosis, myocardial infarction, and stroke following PCI [42].

### Special Population

#### *AF and CKD*

Dosing of NOACs in patients with AF with CKD is mentioned in Table 6 [42].

**Table 6** Dosing of NOACs in patients with AF with CKD [42]

CKD stage	eGFR	Rivaroxaban	Apixaban	Dabigatran	Edoxaban
Stage 1	> 95 ml/min	20 mg OD	2.5 mg BD or 5 mg BD	150 mg BD	60 mg <sup>#</sup>
Stage 2	50–94 ml/min				60 mg
Stage 3	30–49 ml/min	15 mg OD		150 mg BD or 110 mg BD (high bleeding risk)	30 mg
Stage 4	15–29 ml/min	15 mg OD*	2.5 mg BD*	DO NOT USE	30 mg*
Stage 5	Dialysis	DO NOT USE			

\*Use with caution

<sup>#</sup>Use with caution in supranormal renal function

Independently of AF, CKD is a prothrombotic and prohemorrhagic condition and AF may accelerate CKD progression. In AF patients, renal function can deteriorate over time, and worsening CrCl is a better independent predictor of ischemic stroke/systemic embolism and bleeding than renal impairment per se [56]. Choose NOAC based on (a) renal function (CrCl), (b) drug pharmacokinetics, (c) patient's characteristics.

All four NOACs produced comparable results in the primary efficacy endpoints (stroke and SEE) and the primary safety endpoint (major bleeding) across different stages of renal function. The only exception was found in the ARISTOTLE trial. Apixaban seems to produce less bleeding compared to warfarin in patients with an eGFR < 50 ml/min than in those with a higher eGFR ( $p$  for interaction 0.030). In patients with mild-to-moderate CKD (CrCl 30–49 ml/min), the safety and efficacy of NOACs versus warfarin were consistent with patients without CKD in landmark NOAC trials, hence the same considerations for stroke risk assessment and choice of oral anticoagulant may apply. Clearance of NOACs from the body is dependent on renal function, which should be assessed regularly. Of the oral factor Xa drugs, rivaroxaban has 35% renal clearance while apixaban has 27% renal clearance and edoxaban has 50% renal excretion. The renal

clearance of warfarin is < 1% and hence it may be safe for patients with severe CKD [57].

Patients with CrCl 15–29 ml/min: RCT-derived data on the effect of VKA or NOACs are lacking. Data from observational studies conclude possible bleeding risk reduction in patients with ESRD taking a NOAC compared with VKA. There is no solid evidence for a reduction in embolic events with either NOACs or VKAs. For patients with AF after kidney transplantation, there is no data on OAC use in such patients. The prescription and dosing of NOACs should be guided by the estimated glomerular filtration rate of the transplanted kidney and taking into account potential interactions with concomitant medication. NOACs (except apixaban) should be avoided in such patients, while VKAs may be preferable [58].

#### **The Elderly and Frail with AF**

NOACs appear to have a better overall risk–benefit profile compared with warfarin [42]. An Indian consensus recommended that age should not be a limiting factor for use of NOACs. In AF trials, NOACs were more effective than conventional therapy in prevention of stroke or systemic embolism in an elderly population with AF [28]. In one study, anticoagulation therapy significantly increased long-term

overall survival (OS) without increasing risk of clinically relevant bleeding in patients with AF and sinus rhythm (SR) [59]. In another cohort study with patients  $\geq 75$  years (30,401), standard and reduced dose NOACs had similar risks of stroke as warfarin and lower or similar risks of bleeding in patients with AF. Thus, NOACs seem to be a safe oral anticoagulant in elderly patients [60].

## NOAC IN PATIENTS WITH HEPATIC IMPAIRMENT AND AF/VTE

Like other disease states noted above, patients with hepatic impairment are at increased risk of bleeding complications and thrombotic events. Alterations in hepatic function affect NOAC biotransformation to varying extents. Restrictions for the use of NOACs in patients with hepatic impairment are based on the Child–Pugh classification system and exclusion criteria applied in pivotal trials (Table 7) [61].

## NOAC IN PATIENTS WITH OBESITY AND AF/VTE

### Obesity and AF

While obesity is an independent risk factor for AF, the presence of both comorbidities is becoming common. The pharmacokinetics of anticoagulants is altered in obese patients resulting in subtherapeutic serum drug concentrations causing suboptimal efficacy. Drugs with long half-lives and large volume of distribution ( $V_d$ ) get affected by higher BMI while drugs with shorter  $t_{1/2}$  and small  $V_d$  may be less affected by adiposity. In obese patients, the efficacy of NOACs over warfarin is less defined

and has the potential for causing subtherapeutic anticoagulation and lower efficacy. The subgroup analysis of RE-LY, ENGAGE-AF TIMI 48, ARISTOTLE, and ROCKET-AF trial showed that NOAC has similar efficacy compared to warfarin for reducing stroke in obese patients, but major bleeding was similar or higher with NOACs [62]. Results of NOAC in AF and obesity trials are mentioned in Table 8.

In a retrospective analysis, in patients with NVAf, NOACs had better effectiveness and safety compared to warfarin across all BMI categories (underweight and morbidly obese patients) [63]. In a meta-analysis, NOAC was not statistically different from VKA in reducing stroke/SE with RR of 0.85 in morbidly obese patients with atrial fibrillation. Also, major bleeding risk was lower in the NOAC groups with RR of 0.62. Thus, using NOACs in morbidly obese patients may be considered on a case-by-case basis, but more studies are needed to make a robust recommendation [64]. Evidence suggests that NOACs are as effective, if not superior, to warfarin for preventing stroke in obese patients with AF.

### Obesity and VTE

In obese patients with acute VTE, there was no differences VTE recurrence (6.5 vs. 6.4%,  $p = 0.63$ ), recurrence of PE (3.7 vs. 3.8%,  $p = 0.94$ ), or DVT (3 vs. 3.5%,  $p = 0.56$ ) between treatment with NOACs and warfarin. Bleeding was similar for both, NOAC and warfarin groups (1.7 vs. 1.2%,  $p = 0.31$ ) [65]. Another observational study demonstrated NOAC to be effective and safe in morbid obese patients even after intermediate- or high-risk PE [65].

Recommendations from The International Committee on Thrombosis and Haemostasis (ISTH) Scientific and Standardization

**Table 7** NOAC in different stages of hepatic impairment [61]

Child–Pugh category	Rivaroxaban	Apixaban	Dabigatran	Edoxaban
A	No dose reduction	No dose reduction	No dose reduction	No dose reduction
B	Contraindicated	Use with caution	Use with caution	Use with caution
C		Contraindicated	Contraindicated	Contraindicated



**Table 8** Clinical trials of AF and obesity

Landmark trial	Patient characteristics	No. of enrolled obese patients	Results			
RE-LY	BMI ≥ 36 kg/m <sup>2</sup>	1787	Outcome	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
		3099				
	Weight > 100 kg	Total N = 18,114	Stroke/SEE	1.2%	0.9%	1.3%
ROCKET-AF	BMI ≥ 30 kg/m <sup>2</sup>	5206	Outcome	Obese subgroup	Nonobese subgroup	
		1898				
	BMI ≥ 35 kg/m <sup>2</sup>	Total N = 18,201	Stroke/SEE	1.88%	2.93%	HR 0.65
ARISTOTLE	BMI ≥ 30 kg/m <sup>2</sup>	7159	Outcome	Apixaban	Warfarin	
		982				
	Weight > 120 kg	Total N = 18,201	Stroke/SEE	0.97%	1.28%	HR 0.76
ENGAGE-TIMI	BMI ≥ 30 kg/m <sup>2</sup>	8457	Outcome	Normal BMI	Severely obese	Very severely obese
		1149				
	BMI > 40 kg/m <sup>2</sup>	148	Stroke/SEE	2.3%	HR 0.68	HR 0.54
	BMI > 50 kg/m <sup>2</sup>	Total N = 21,105	Major bleeding	2.9%	HR 1.18	HR 1.28

BMI body mass index, SEE systemic embolic events

Committee (SSC) Subcommittee on Control of Anticoagulation (2021) recommends the use of any NOAC in patients with BMI up to 40 kg/m<sup>2</sup> or weight 120 kg [66]. For patients with BMI > 40 kg/m<sup>2</sup> or weight > 120 kg, the guideline recommend that the individual NOACs should be used as mentioned in Table 9.

A meta-analysis comprising real-world observational data concludes that the use of NOACs in morbidly obese patients (bodyweight of > 120 kg or BMI > 40 kg/m<sup>2</sup>) is effective and safe. It supports the current practice of using NOAC analogs as an alternative to warfarin in this cohort of patients [67].

## HOW TO CHOOSE BETWEEN NOACS

Since there are no head-to-head comparisons of NOACs, it is extremely difficult to provide definitive recommendations on choice of NOAC. Thus, patient characteristics, drug tolerability, and cost may be considered while selecting a NOAC for a specific patient. Risk of ischemic stroke, bleeding, history of stroke, gastrointestinal (GI) upset, past GI bleed and renal impairment are a few of the factors that determine the choice of NOAC (Table 10) [68].

**Table 9** Recommendations for use of NOAC in obese patients [66]

Indication	Recommendation
Treatment of VTE	<p>Standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight</p> <p>Fewer supportive data exist for apixaban than rivaroxaban</p> <p>VKA, weight-based LMWH (per manufacturers' recommendations), and fondaparinux are also options</p> <p>Not to use dabigatran, edoxaban, or betrixaban given unconvincing data for dabigatran, and lack of clinical or PK/PD data for edoxaban and betrixaban</p>
Primary prevention of VTE	<p>Standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight</p> <p>Not to use dabigatran, edoxaban, or betrixaban given unconvincing data for dabigatran, and lack of clinical or PK/PD data for edoxaban and betrixaban</p>
Post bariatric surgery—treatment or prevention of VTE	<p>Initiate patients on parenteral anticoagulation in the early postsurgical phase</p> <p>Not to use DOAC (because of concerns of decreased absorption)</p> <p>Switching to VKA or DOAC may be considered after at least 4 weeks of parenteral treatment, and if so, suggest obtaining a DOAC trough level to check for drug absorption and bioavailability</p>

## SWITCHING BETWEEN NOACS

It is not uncommon to switch from one anticoagulant to another. The decision to switch and type of anticoagulant depends on factors such as cost, comorbidity, patient preference, hospitalization, thrombotic complications, bleeding complications, or procedures [61]. The scenarios that exist are explained in Table 11.

Monitoring of anticoagulant effect is important before, during, and after switching. INR should be measured just before the NOAC dosing and re-tested 24 h after the last NOAC dose (i.e., sole warfarin therapy) to assure adequate anticoagulation. Since NOACs may have an additional influence on INR during the overlap phase, closely monitor INR within the first month until stable values are attained (i.e., three consecutive measurements between 2 and 3) [69].

## PERIOPERATIVE MANAGEMENT OF PATIENTS ON ANTICOAGULANTS

The clinicians must assess the patient's thromboembolic risk:

- Bleeding risks: (a) patient-specific (b) procedure-specific.
- Understand the NOAC's pharmacological properties.
- Assess the patients' renal function.
- Determine the timing of the anticoagulant interruption.
- Determine whether to use bridging anticoagulation [70].

### NOAC Interruption

A patient-centered approach to NOAC interruption that is anchored on the procedure-related bleed risk, NOAC type, and patient renal function is shown in Fig. 6.

**Table 10** Factors to consider when choosing an oral anticoagulant [68]

Specific patient characteristics	Considerations	Choice of NOAC
High risk of bleeding, e.g., HAS-BLED $\geq 3$	Consider agent/dose with the lowest incidence of bleeding	Dabigatran 110 mg Apixaban
Previous GI bleeding or high risk	Consider agent the lowest reported incidence of GI bleed	Apixaban
High risk of ischemic stroke, low bleeding risk	Consider agent/dose with the best reduction of ischemic stroke	Dabigatran 150 mg
Previous stroke (secondary prevention)	Consider best investigated agent or greatest reduction of secondary stroke	Rivaroxaban Apixaban
CAD, previous MI or high risk for ACS/MI	Consider agent with a positive effect in ACS	Rivaroxaban
Renal impairment	Consider agent less dependent on renal function	Apixaban Rivaroxaban
GI upset/disorders	Consider agent/dose with no reported GI effects	Apixaban
Patient preference	Consider once daily formulation	Rivaroxaban

Doses may need to be adjusted for interactions, weight, and co-morbidities

*ACS* acute coronary syndrome, *AF* atrial fibrillation, *CAD* coronary artery disease, *GI* gastrointestinal, *HAS-BLED* hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile international normalized ratio, elderly ( $\geq 65$  years), drugs/alcohol concomitantly (1 point each), *MI* myocardial infarction

The Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) cohort study included patients with AF who had NOAC interruption for elective surgery/procedure. The PAUSE study had the following approach: 1 full day off NOAC if low bleed risk; 2 full days off NOAC if high bleed risk (in addition to no NOAC intake on the procedure day). The post-procedure resumption of NOAC mirrored pre-procedure management in that the NOAC was resumed after 1 day (at least 24 h) after a low bleed risk procedure, and resumed after 2 days after a high bleed risk procedure. The initiation of a prophylactic dose anticoagulant (LMWH or NOAC) was considered in patients at high bleeding risk in whom a delay of full-dose anticoagulation was warranted. Patients that had a simple standardized perioperative management strategy without heparin bridging or measurement of coagulation function had low

rates of major bleeding and arterial thromboembolism [71]. NOAC interruption and restarting regimen during elective procedures is mentioned in Table 12 [61].

### Does NOACs Require Bridging Anticoagulant?

NOACs do not require parenteral overlapping or “bridging” anticoagulants peri-procedurally. NOACs (dabigatran, rivaroxaban, apixaban, edoxaban) have relatively shorter time-to-onset and half-lives (about 12 h) and are easier to discontinue and resume rapidly [70]. Hence, LMWH/heparin bridge was used as a bridging anticoagulant in RE-COVER and RE-COVER II trials, whereas no bridging anticoagulant was used in rivaroxaban trials (EINSTEIN PE, EINSTEIN DVT), apixaban (AMPLIFY), and edoxaban trial (Hokusai-VTE). The rapid offset and

**Table 11** Switching between NOACs and other anticoagulants [61]

From	To	Action
VKA	NOAC	Stop VKA and start NOAC once INR is < 2 or lower INR limit of the therapeutic range
Dabigatran	VKA	CrCl > 50 ml/min: start VKA and stop dabigatran 3 days later CrCl 31–50 ml/min: start VKA and stop dabigatran 2 days later CrCl 15–30 ml/min: start VKA and stop dabigatran 1 day later
Rivaroxaban	VKA	Start VKA and stop NOAC 3 days later
Apixaban		OR For continuous anticoagulation: Stop NOAC and start LMWH and VKA at the time NOAC would have been due, then stop LMWH when INR is within the therapeutic range
Edoxaban		Start VKA and stop NOAC 3 days later OR For continuous anticoagulation: For 60 mg dose: reduce: reduce dose to 30 mg and start warfarin concomitantly. Stop edoxaban when INR > 2 For 30 mg dose: reduce dose to 15 mg and start warfarin concomitantly. Stop edoxaban when INR > 2
Betrixaban	VKA	Start VKA and stop NOAC when INR > lower limit of the therapeutic range
NOAC	NOAC	Stop the current NOAC regimen and begin the new NOAC agent at the time the next dose of NOAC is due
NOAC	Parenteral anticoagulant	Stop NOAC and start parenteral anticoagulation at the same time that the next dose of NOAC would have been given
Parenteral anticoagulant	NOAC	Intravenous: Start NOAC 0 to 2 h after stopping UFH Subcutaneous: Stop LMWH and start NOAC at the same time that the next dose of LMWH would have been given

*CrCl* creatinine clearance, *INR* international normalized ratio, *LMWH* low molecular weight heparin, *VKA* vitamin K antagonist, *UFH* unfractionated heparin

onset of rivaroxaban negate the need for bridging anticoagulation.

### Restarting NOAC Post-procedure

Restarted 2 days after a high bleeding risk procedure and restarted 1 day after a low/moderate bleeding risk procedure.

Since the anticoagulant effect of NOACs peaks within a few hours, it is safe to wait for 24–72 h post-procedure before starting the full dose. The restarting dose will be similar to the pre-op dose. Administer a parenteral anticoagulant (low-dose LMW heparin or fondaparinux) regimen (for example enoxaparin 40 mg daily) until the NOAC is resumed (if there is an increased risk of VTE). Dosage adjustment is not

Bleeding risk of the procedure	3 days pre-op	2 days pre-op	1 day pre-op	Day of surgery	1 day post-op	2 days post-op	3 days post-op
<b>Low risk</b>	✓	✓	✗	✗	✓	✓	✓
<b>High risk</b>	✓	✗	✗	✗	✗	✓	✓

No major bleeding

**Fig. 6** Timing for interruption of a NOAC before and after elective surgery [71]. \*Regular NOAC dose. Note: ✓ indicates continue NOAC; ✗ indicates stopping NOAC

required in patients with moderately impaired kidney function (CrCl 30–50 ml/min) [72].

### ANTIDOTES OR REVERSIBILITY AGENTS: ARE THEY NEEDED?

Reversal agents are indicated in patients with major bleed. Non-major/minor bleed—reversal agents not required, and withholding the next NOAC doses is sufficient. The choice of NOAC should not be based on the availability of its respective reversal agents.

Anticoagulant reversal is a critical step in the management of patients with life-threatening bleeding who are taking an anticoagulant. A specific antidote or reversal agent may be considered in severe or life-threatening bleeding in patients receiving NOAC (Fig. 7). There are two types of reversal agents—non-specific and specific reversal agents. FDA-approved reversal agents for NOACs are idarucizumab for dabigatran and andexanet alfa for apixaban and rivaroxaban. Their higher cost and limited availability remain a concern (Table 13; Fig. 8) [72]. A larger amount of clinical data on reversal agents should be available with their increased usage.

### DOSING ERRORS

In case of missed dose, the forgotten dose can be taken up to 6 h or up to 12 h after the scheduled intake for a BD or OD regimen, respectively. If this is not possible, the dose should be skipped, and the next scheduled dose taken. In case of a double dose on a BD regimen, the next planned dose can be skipped and restarted BD after 24 h while in OD dosing, a normal regimen can be continued. In case of overdose, dabigatran can be removed via dialysis. Rivaroxaban and apixaban are not dialyzable, and hence use reversal agents [73].

### UNDERDOSING

Elderly patients with AF should be prescribed anticoagulant therapy, unless contraindicated. Though, the risk of bleeding is higher in the elderly, it is dependent on a patient’s characteristics and not on whether the patient is receiving anticoagulant or not. The bleeding risk should be minimized rather than contraindicating or underdosing the anticoagulant. Various studies indicate that inappropriate prescription of NOACs is not uncommon, especially underdosing [74]. In the SAGE-AF study, underdosing of NOACs was more common than overdosing. Factors that influence prescription of guideline-nonadherent doses may be old age,

**Table 12** When to interrupt and restart NOAC therapy during elective procedures [61]

Bleeding risk of the procedure	Parameter	Rivaroxaban	Apixaban	Dabigatran	Edoxaban
Minor	Recommended to not stop in most minor surgical procedures				
	STOP	12–24 h before procedure			
	RESTART	6 h after intervention			
Low risk	STOP	24–96 h before procedure			
	CrCl $\geq$ 80 ml/min	STOP $\geq$ 24	STOP $\geq$ 24	STOP $\geq$ 24	STOP $\geq$ 24
	CrCl $\leq$ 50–79 ml/min	STOP $\geq$ 24	STOP $\geq$ 24	STOP $\geq$ 36	STOP $\geq$ 24
	CrCl $\leq$ 30–49 ml/min	STOP $\geq$ 24	STOP $\geq$ 24	STOP $\geq$ 48	STOP $\geq$ 24
	CrCl $\leq$ 15–29 ml/min	STOP $\geq$ 36	STOP $\geq$ 36	Not indicated	STOP $\geq$ 36
	CrCl $\leq$ 15 ml/min	Consider measuring drug activity to determine absence of drug effect			
	RESTART	$\geq$ 24 h after intervention			
High risk	STOP	48–96 h before procedure			
	CrCl $\geq$ 80 ml/min	STOP $\geq$ 48	STOP $\geq$ 48	STOP $\geq$ 48	STOP $\geq$ 48
	CrCl $\leq$ 50–79 ml/min	STOP $\geq$ 48	STOP $\geq$ 48	STOP $\geq$ 72	STOP $\geq$ 48
	CrCl $\leq$ 30–49 ml/min	STOP $\geq$ 48	STOP $\geq$ 48	STOP $\geq$ 96	STOP $\geq$ 48
	CrCl $\leq$ 15–29 ml/min	STOP $\geq$ 48	STOP $\geq$ 48	Not indicated	STOP $\geq$ 48
	CrCl $\leq$ 15 ml/min	Consider measuring drug activity to determine absence of drug effect			
	RESTART	$\geq$ 48–72 after intervention			

Minor-bleeding-risk interventions: dental, cataract, glaucoma, endoscopy without biopsy or resection, superficial surgery; low-bleeding-risk interventions: endoscopy with biopsy, prostate biopsy, bladder biopsy, pacemaker or implantable cardioverter-defibrillator implantation, noncoronary angiography, electrophysiological study/catheter ablation; high-bleeding-risk intervention: major surgery, spinal puncture or placement of spinal/epidural catheter, other situations in which complete hemostasis is required

CrCl Cockcroft–Gault creatinine clearance; and NA not applicable

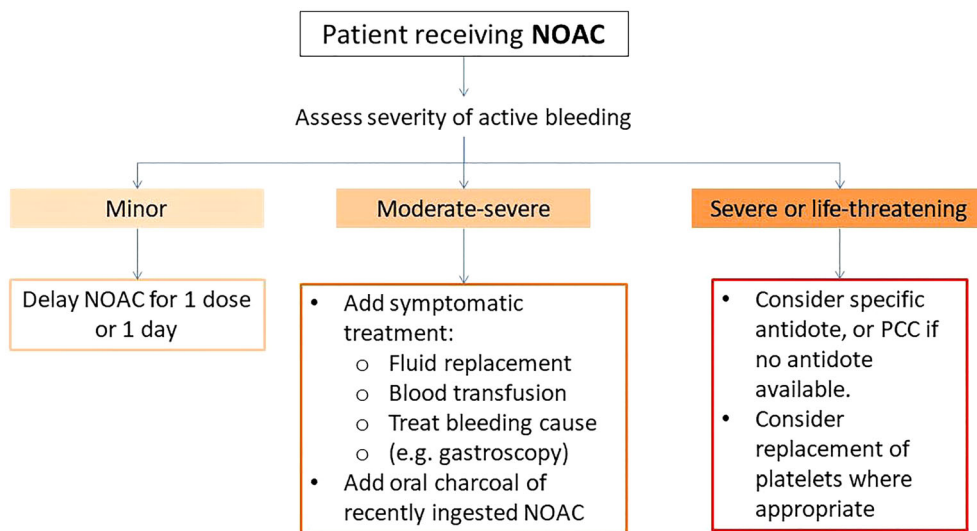
\*Skip 1 dose of dabigatran or apixaban; no dose of edoxaban or rivaroxaban is skipped

†Has not been studied

higher bleeding risk, renal failure or lack of familiarity with dosing guideline [75].

Underdosing of NOACs has been observed in several countries [74, 76–80]. Dosing of rivaroxaban (adjusted according to kidney function) may be simpler than that of other NOACs, which is slightly more limited by various factors (creatinine, weight, age, treatment with P-glycoprotein inhibitors). The main factors associated with underdosing are advanced

age, kidney failure, co-morbidities and having a high risk of bleeding and thromboembolic events. Doctors must not choose lower dose of NOACs just out of a fear of bleeding (thus ignoring the risk of stroke) [74]. Under-dosing of NOACs in patients with AF may be associated with reduced effectiveness for stroke prevention, with similar or even increased bleeding than with the standard dose [81]. Anticoagulation monitoring enables personalized and



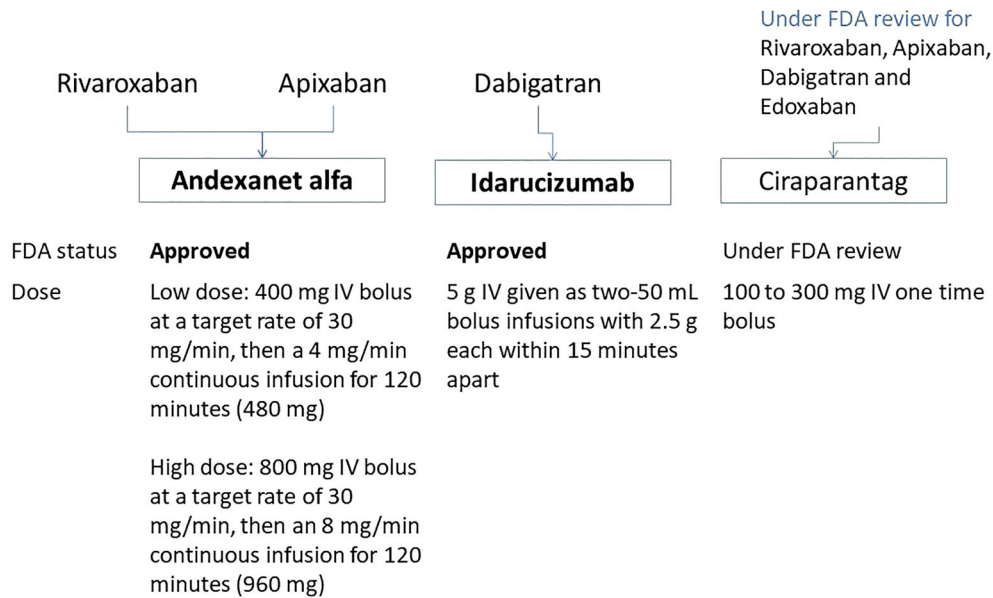
**Fig. 7** Management of active bleeding in patients receiving NOAC anticoagulation [42]. *FFP* fresh frozen plasma, *INR* international normalized ratio, *i.v.* intravenous, *NOAC* non-vitamin K antagonist oral anticoagulant,

*OAC* oral anticoagulation therapy, *PCC* prothrombin complex concentrates, *VKA* vitamin K antagonist

**Table 13** Characteristics and dosing of reversal agents [72]

Parameter	Andexanet alfa	Idarucizumab	Ciraparantag
FDA status	Approved	Approved	Under FDA review
Dose	Low dose: 400 mg IV bolus at a target rate of 30 mg/min, then a 4 mg/min continuous infusion for 120 min (480 mg) High dose: 800 mg IV bolus at a target rate of 30 mg/min, then an 8 mg/min continuous infusion for 120 min (960 mg)	5 g IV given as two 50-ml bolus infusions with 2.5 g each within 15 min apart	100–300 mg IV one time bolus
Structure	Modified factor Xa decoy protein	Monoclonal antibody fragment	Synthetic water-soluble molecule
Mechanism	Binds to the active site of factor Xa inhibitors	Binds free and thrombin-bound dabigatran	Direct binding to anticoagulants
Onset of action	2–5 min	10–30 min	10 min
Half-life	1 h	45 min	45 min

\*Based on currently available data



**Fig. 8** Dosing regimen of NOAC reversal agents [72]

appropriate off-label under-dosing in NVAF patients on rivaroxaban or apixaban through the measurement of peak plasma concentration (PC) during NOAC use [82].

## NOAC IN OTHER CARDIAC CONDITIONS

The NOACs are contraindicated in atrial fibrillation patients with rheumatic mitral stenosis or mechanical heart valves [83]. Catheter ablation for AF is an unknown and neglected aspect that needs to be highlighted. A prospective study including NOAC-treated patients requiring AF ablation showed that uninterrupted NOAC therapy led to highly variable and unpredictable initial level of anticoagulation before catheter ablation. Cardiologists, electrophysiologists, and intensivists must be aware of the evidence gaps regarding intraprocedural anticoagulation in uninterrupted NOAC-treated patients. Vigilance should be reinforced regarding bleeding and thrombosis risk while waiting for more laboratory and clinical data for intraprocedural anticoagulation [84].

## DRUG–DRUG INTERACTIONS

Drug–drug interactions of NOACs are respective recommendations are mentioned in Table 14.

## MEASURING NOAC

Measuring NOAC levels with dedicated tests before surgical or invasive procedures is of paramount importance for patient safety. The tests help to rule in or out clinically relevant concentrations of residual drugs. Although NOAC do not need routine dose adjustment based on laboratory testing, the measurement of their anticoagulant effect may be useful in special situations such as (a) at the time of adverse events (hemorrhage or thrombosis), (b) before antidotes administration, (c) to make decision on thrombolytic therapy in ischemic stroke patients. Whenever drug-to-drug interaction is suspected, (d) in patients with extreme body weight [86].

### Best Tests to Monitor NOAC Levels?

Routine anticoagulation with assays such as prothrombin time (PT), activated partial



**Table 14** Summary of recommendations for drug–drug interactions with NOACs and selected medications [85]

Interacting agent	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
	P-gp and strong CYP3A inhibitors and inducers	CYP3A4 and P-gp inhibitors and inducers	Anticoagulants, antiplatelets, thrombolytics, and selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs)	P-gp inducers
Antiarrhythmic agents				
Dronedarone	Avoid combination if CrCl < 80 ml/min	Combination is considered acceptable	Reduce dose of edoxaban by 50%	Administer 2 h before dronedarone Reduce dose to 75 mg twice daily for CrCl 30–50 ml/min Avoid use if CrCl < 30 ml/min
Amiodarone	Avoid use if CrCl < 80 ml/min	Combination is considered safe	Combination is considered safe	Combination considered safe if CrCl > 50 ml/min Avoid combination if CrCl < 50 ml/min for VTE and < 30 ml/min for NVAf
Calcium-channel blockers				
Verapamil	Avoid use if CrCl < 80 ml/min	Combination is considered safe	Combination is considered safe	Avoid use if CrCl < 30 ml/min for NVAf and < 50 ml/min for VTE
Diltiazem	Avoid use if CrCl < 80 ml/min	Combination is considered safe	Combination is considered safe	Combination is considered safe
Enzyme inducers				

**Table 14** continued

Interacting agent	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Phenytoin, carbamazepine, primidone, rifampin, phenobarbital, St. John's wort	Avoid combination; consider warfarin			

*CrCl* creatinine clearance, *NVAF* nonvalvular atrial fibrillation, *VTE* venous thromboembolism

thromboplastin time (aPTT), or thrombin time (TT) may provide limited information of drug concentration in cases of acute bleeding, emergent surgical intervention, need for intravenous thrombolysis, acute intracerebral bleeding, and suspected anticoagulant overdose. Point-of-care testing (POCTs) can offer quick information on NOAC concentration in such instances, allowing for emergency reversal. To detect the plasma concentrations of factor Xa inhibitors, anti-factor Xa chromogenic assays are available, and utilizing these assays, the absence of factor Xa activity can reliably rule out the presence of clinically significant drug levels [72].

### Routine NOAC Monitoring?

Although NOAC drug levels can be accurately measured, information on the optimal level in specific patient groups (e.g., the elderly, the renally impaired, and those at high risk of bleeding), the appropriate dose adjustment to achieve expected levels, and whether routine laboratory monitoring and dose adjustment will improve clinical outcomes are all lacking. Unmonitored NOAC medication is at least as effective and safe as monitored warfarin therapy, with lower risks of cerebral hemorrhage and mortality, according to evidence from patients with atrial fibrillation who were randomized to NOACs or warfarin. There has to be more research done to see if routine laboratory monitoring is beneficial to patients. Clinicians should continue to administer NOACs in fixed

doses without routine monitoring until more data becomes available [87].

### Strengths and Limitations

Clinicians and policymakers must see this document to help reduce the gap between clinical practice and scientific evidence. It offers expert recommendations and newer treatment options for clinicians who are uncertain about prescribing the right NOAC in a specific situation. The principal benefit of this document is to improve the quality of clinical decisions. Although we assembled a panel of clinicians from academic and community settings, as well as urban and rural settings, it does not stand the same for the diverse healthcare practice in India that ranges from poor to very good medical service. Secondly, these recommendations do not include a cost–benefit analysis. Thirdly, the expert group was not multi-disciplinary, and finally, the development of this practical guideline was not as rigorous as compared to a clinical practice guideline (the clinical evidence was not graded).

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