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Review

Periprocedural management of anticoagulation in patients taking novel oral anticoagulants: Review of the literature and recommendations for specific populations and procedures

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ABSTRACT

An increasing number of individuals are on novel oral anticoagulants (NOAC) for anticoagulation instead of vitamin K antagonists (VKA) and roughly 10% of these individuals will require interruption of these agents for procedures annually. Recent evidence surrounding bridging as well as the FDA approval of a new NOAC call for a comprehensive review and update regarding periprocedural NOAC management.

The periprocedural management of NOACs involves striking a balance between the risks of bleeding and thromboembolism associated with interruption, bridging, and reinitiation of anticoagulation. NOACs have a distinct pharmacokinetic advantage in this setting with their quick onset and elimination from the body. Procedures at low risk for bleeding do not require interruption and can be scheduled at the start of the next dosing interval. Procedures at moderate-high risk of bleeding require interruption of NOAC for 5 half lives prior to the procedure to allow for adequate elimination of the drug. In light of new evidence highlighting the risks of bleeding, and given shorter "unprotected" times with NOAC interruption versus VKA, patients at low-moderate risk for thromboembolism should not be bridged when "unprotected" time is less than 96 h. For patients at high risk for thromboembolism, individual patient and surgical factors need to be considered before the decision to bridge is made. The benefit of bridging these patients who have a considerable risk of bleeding may not outweigh the benefits. Focused randomized studies on periprocedural management of NOACs are urgently needed.

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1. Background

An estimated 2.5 million Americans are on oral anticoagulation therapy and ~10% require cessation of anticoagulation for percutaneous and surgical procedures every year [1]. While there is clear consensus regarding the periprocedural management of Vitamin K antagonists (VKA) [2], the evidence and recommendations surrounding the periprocedural management of novel oral anticoagulants (NOAC) are more complex and ambiguous. This is, in part, due to the number of agents available on the market – dabigatran, rivaroxaban, apixaban, and edoxaban – as well as their individually unique pharmacokinetic profiles [3–6]. NOAC use has also increased dramatically since with ~1/3 of patients with atrial fibrillation (AF) using them for stroke prophylaxis [7]. Cost-effective analyses between NOAC and VKA have shown that NOAC can be a cost-effective alternative to VKA, particularly in those with moderate-high risk of stroke and in areas where warfarin time in therapeutic range is low [8]. In recent years, several review papers have been published regarding this topic [9,10]. However, in light of recent studies pertaining to the topic of periprocedural anticoagulation and the entrance of edoxaban into the United States market, a thorough review of this topic with evidence-based recommendations will make navigating around the pitfalls of NOAC management in the periprocedural setting less formidable [11–13].

1.1. Efficacy of NOACs for stroke prophylaxis in AF

The annual incidence of stroke in patients with AF can vary widely between 1.9% and 18.2% based on the CHADS2 risk score [14]. Maintaining the international normalized ratio (INR) between 2 and 3 with warfarin reduces the risk of stroke, with an annual incidence of 1.6–2.2% per year [3–6]. All NOACs are at least non-inferior to warfarin in terms of efficacy, reducing the annual incidence of stroke to 1.2–1.7% per year [3–6]. In terms of major bleeding, all NOACs are also as least as safe as warfarin [3–6].

Abbreviations: NOAC, novel oral anticoagulant; VKA, vitamin K antagonist; AF, atrial fibrillation; VTE, venous thromboembolism; aPTT, activated partial thromboplastin time; LMWH, low-molecular weight heparin; C_{max}, peak concentration; T_{max}, time of peak concentration; AUC, area under curve; ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; PPM, permanent pacemaker; ICD, implantable cardioverter defibrillator.

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Table 1
Pertinent pharmacologic characteristics for currently available NOACs compared to warfarin.

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Warfarin
Pharmacology	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Vitamin K antagonist
Time to peak concentration	1.5 h [22]	1.9 h [20]	1.0–3.3 h [24,105]	1.3 h [21]	2–6 h, but onset of action is 3 days [106]
Half life	12–14 h [26]	7–8 h [23]	11 h [19]	9 h [21]	35 h [106]
CrCl >80 mL/min					
CrCl 50–80 mL/min	16.6 h [38]	8.7 h [36]	14.2 h [37]	12.9 h [11]	35 h [106]
CrCl 30–50 mL/min	18.7 h [38]	9.0 h [36]	18.2 h [37]	16.5 h [11]	35 h [106]
CrCl 15–30 mL/min	27.5 h [38]	9.5 h [36]	N/A	17.5 [11]	35 h [106]
Dietary Restrictions	None [28]	Take with evening meal [33]	None [32]	None [12]	Avoid inconsistent intake of vitamin K [106]
Nonvalvular AF dose	150 mg PO BID [28]	20 mg PO daily [33]	5 mg PO BID [32]	60 mg PO daily [12]	Requires therapeutic drug monitoring [106]
Normal VTE dose	150 mg PO BID (after 5–10 days of parenteral anticoagulation) [28]	20 mg PO daily (after 15 mg BID × 21 days) [33]	5 mg PO BID (after 10 mg PO BID × 7 days) [32]	60 mg PO daily [12]	Requires therapeutic drug monitoring [106]
Renal dosing	For CrCl between 15 and 30 mL/min, dose for nonvalvular AF is 75 mg PO BID; not recommended when CrCl is <15 mL/min; avoid use in VTE when CrCl <30 mL/min [28]	Avoid use when CrCl <30 mL/min [33]	For non-valvular AF, reduce dose to 2.5 mg PO BID in patients who have 2 of the following 3 criteria: 1) Age >80 years 2) Body weight ≤60 kg 3) Serum creatinine ≥1.5 mg/dL No renal dosing adjustment for VTE treatment [32]	For CrCl between 15 and 50 mL/min, decrease dose to 30 mg PO daily; avoid use when CrCl <15 mL/min or >95 mL/min	Dosing dependent on therapeutic drug monitoring [106]
Drug interactions	P-glycoprotein inhibitors [28]	P-glycoprotein and CYP3A4 inhibitors and inducers [33]	P-glycoprotein and CYP3A4 inhibitors and inducers [32]	P-glycoprotein inhibitors [12]	CYP2C9, CYP1A2, CYP3A4 inhibitors and inducers [107]
Dialysis	62–68% of drug removed [38]	Not effective [41]	Not effective [32]	Not effective [42]	Not effective [106]

CrCl — creatinine clearance, BID — twice daily.

1.2. Efficacy of NOACs for the treatment of venous thromboembolism (VTE)

In the initial treatment of VTE, all NOACs were at least non-inferior to warfarin with an incidence of recurrent VTE events ranging between 2.1% and 3.2% at 6–12 months of treatment [15–18]. Similarly, all NOACs were at least as safe as warfarin in terms of major bleeding [15–18].

1.3. Pharmacology of NOACs

All NOACs are synthetic, reversible inhibitors of key factors involved in the coagulation cascade. Whereas dabigatran targets factor IIa (thrombin), apixaban, rivaroxaban, and edoxaban all target factor Xa. After single-dose oral administration, all NOACs achieve peak serum drug concentration (C_{max}) within 1–3 h (T_{max}) [19–22]. All NOACs are eliminated by first order kinetics and are cleared from the body within 5 half-lives after the last dose, predominantly via renal excretion [19–22]. The half-lives range from 7 to 8 h for rivaroxaban to 12–14 h for dabigatran (Table 1), ensuring all NOACs are cleared within 48–72 h after discontinuation in those with normal renal and hepatic function [19–24]. However, the anticoagulation effect of the NOAC becomes clinically irrelevant much sooner. Even dabigatran, which has the longest half-life among NOACs, loses much of its anticoagulation potency 24 h after the last dose with drug concentration dropping to ~25% of C_{max} [22].

1.4. Laboratory monitoring

All the currently available NOACs have predictable pharmacokinetics and routine laboratory monitoring is neither employed nor recommended to assess efficacy of anticoagulation in day-to-day clinical practice. INR and activated partial thromboplastin time (aPTT) cannot be used in the clinical setting due to low sensitivity and large variability in clotting times between the numerous commercially available reagents [19,25]. Anti-factor Xa assays are more sensitive and less variable, making factor Xa activity the most suitable test to monitor drug concentrations of apixaban [25]. Factor Xa activity also correlated well with plasma concentration of rivaroxaban and edoxaban [20,21]. Dabigatran, however, works downstream of factor Xa in the coagulation cascade and its effect cannot be assessed by factor Xa activity. Ecarin clotting time appears to be the most sensitive and useful measurement of dabigatran's anticoagulation activity [22,26,27]. While the manufacturer does report that aPTT levels can be used to approximate anticoagulant effects, a specific aPTT value appropriate for surgery is not known [28]. An accurate, reliable, and widely available assay is not yet available for this class of medication and would be clinically very useful.

2. General principles guiding periprocedural management of NOACs

The risk-benefit assessment of periprocedural NOAC management is similar to that of VKA. The first step is to determine the bleeding risk of the procedure and compare it to the risk of interrupting or withholding anticoagulation during the time leading up to the procedure. If the risk of interrupting anticoagulation is prohibitively higher than the procedural bleeding risk, anticoagulation should not be interrupted or at least be substituted with a low-molecular weight heparin (LMWH) or unfractionated heparin regimen. For patients on chronic warfarin therapy, the usual practice is to stop warfarin 4–5 days before the anticipated procedure with high risk for bleeding [1]. Bridging is then started in those individuals with moderate-high risk for periprocedural thromboembolism in the form of LMWH or unfractionated heparin [1,2]. Post-procedural warfarin is usually reinitiated on postoperative day 0 as long as hemostasis is achieved [1].

The use of a NOAC offers two distinct pharmacokinetic advantages over a VKA in the periprocedural setting. First and foremost, a NOAC provides concentration-dependent, and therefore, predictable levels of anticoagulation [19–22]. Minor dental, dermatologic, and ophthalmologic

procedures are associated with low bleeding risk and generally do not require interruption of anticoagulation (Fig. 1) [2]. In this setting, the procedure can be thoughtfully scheduled to occur at the next dosing interval, when the trough of drug concentration is anticipated [10]. Additionally, gentle mouth rinse using 10 mL of 5% tranexamic acid is suggested for minor dental procedures [10].

The second pharmacokinetic advantage of NOACs, in the setting of normal renal function, is their rapid clearance from the body. Whereas warfarin is typically stopped 4–5 days before the anticipated procedure, NOACs can be stopped the day prior, allowing up to 48 h (time from last dose until procedure) for drug clearance from the body. This has significant implications when the question of bridging arises, as these individuals would only be "unprotected" for a shorter period of time compared to those on a VKA. However, while bridging is generally not required for NOACs due to this reason [9,10], in some cases, particularly dabigatran use in the setting of severe renal dysfunction when interruption of anticoagulation can be up to 4–5 days, bridging still has a place in the management of patients at high risk for thromboembolism.

A recent registry analysis showed that in 2200 patients who required temporary interruption of VKA for a procedure, the risk of thromboembolic events (myocardial infarction, stroke, systemic embolism, or thrombotic event) was similar between those who received bridging ($n = 592$) vs. those who did not ($n = 1608$) [13]. Moreover, the bleeding risk was substantially greater (1.2% vs. 3.6%, $P < 0.001$) in the bridging group [13]. A similar finding was also demonstrated with dabigatran in a RE-LY trial sub-study [29]. Douketis et al. suggested that all patients at high-risk (>10% annual risk) and some patients at moderate-risk (5–10% annual risk) for procedural thromboembolism should receive bridging anticoagulation [2]. Given a substantially reduced period of unprotected time for the NOACs (24–48 h in most cases) vs. VKA (4–5 days), especially in light of recent data on outcomes with bridging, we do not recommend bridging for those at low to moderate-risk of periprocedural thromboembolism when unprotected times are <96 h. However, in cases of severe renal impairment when unprotected times exceed 96 h due to interruption, bridging can be considered (Fig. 1).

Patients at high risk for thromboembolism (CHADS2 score of 5–6, recent stroke, VTE, or transient ischemic attack within the past 3 months, hypercoagulable state) should be considered for bridging (Fig. 1) [2,14]. As bridging may result in increased bleeding, the patient's bleeding risk should also be carefully considered. In certain patients who are at considerable risk of bleeding, such as those with a HAS-BLED score of >5, the bleeding risk may outweigh the potential benefits of bridging [13,30,31]. The decision to bridge patients at high-risk for thromboembolism should be based on individual surgical and patient characteristics, including the risk of bleeding, as well as length of NOAC interruption.

In summary, the principles of periprocedural NOAC management revolve around the same risk-benefit assessment process used for VKAs. The NOACs offer greater predictability in terms of anticoagulation making them more convenient to use in procedures at low risk for bleeding when the procedure can be scheduled at the start of the next dosing interval. In addition, their rapid clearance from the body results in shorter unprotected times after regimen interruption, which obviates the need for bridging in those at low to moderate risk, and in most patients at high risk for periprocedural thromboembolic events (Fig. 1).

It should be emphasized that presence of mechanical valves was not factored into these recommendations because NOACs are not indicated for use in these patients [12,28,32,33]. In addition, while patients with underlying thrombophilia were included in large phase 3 trials, they only accounted for a small percentage of the population studied [15–18]. There have also been a few case reports documenting therapeutic failure with NOAC when treating patients with antiphospholipid syndrome [34]. Therefore, clinical data for NOAC use in the thrombophilic patient is somewhat limited.

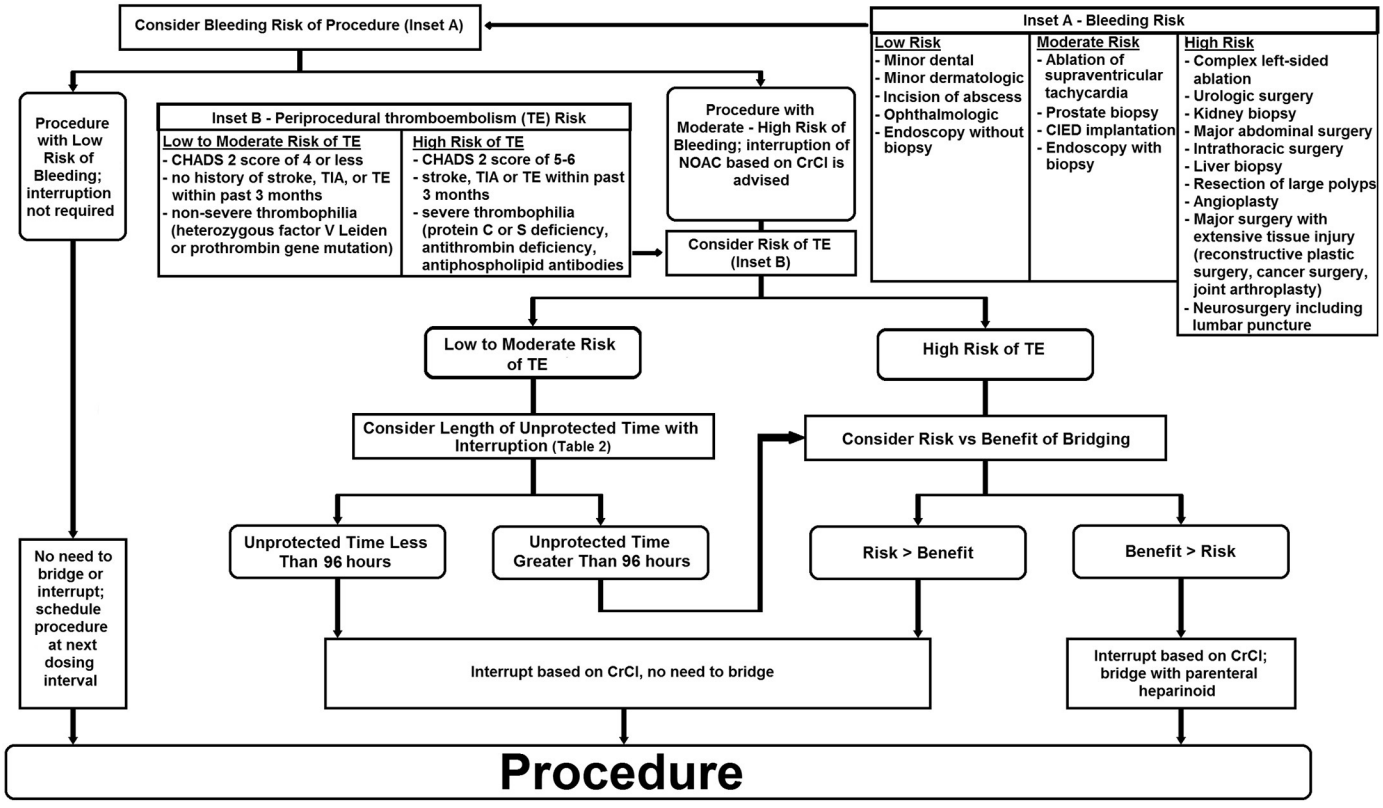

Fig. 1. Algorithm for periprocedural management of NOACs. Inset A shows bleeding risk categories and procedures associated with them whereas Inset B shows the level of periprocedural thromboembolism risk based on patient factors. Refer to Table 2 for interruption time based on creatinine clearance (CrCl).

As no parenteral forms of NOACs are available, another important consideration is the availability of the oral route of administration post-operatively. Rivaroxaban and apixaban tablets may be crushed and administered through a feeding tube [32,33]. Data is not available for crushing edoxaban tablets, and the contents of a dabigatran capsule should not be opened and administered through a feeding tube [12,28]. In cases when the oral route may not be available for several days, especially when the risk of bleeding is low but the risk of thrombosis is high, the use of post-operative bridging with a parenteral anticoagulant should be planned accordingly.

3. Specific agents

3.1. Dabigatran

Manufacturer recommendations suggest that dabigatran be stopped 1–2 days before anticipated surgery if creatinine clearance (CrCl) is >50 mL/min and is consistent with dabigatran's half-life (12–14 h) and the golden rule of 1st order kinetics to wait 5 half-lives before a new steady-state is reached [28]. We recommend that dabigatran be held 1 day before a procedure of moderate bleeding risk and 2 days before a procedure of high bleeding risk (Table 2). As dabigatran is given twice daily, this will allow ~60 h (5 × 12 h or 5 half-lives) to elapse between the time of the procedure and the last administration of dabigatran. Reinitiation of dabigatran is recommended once hemostasis is achieved, and T_{max} (Table 1) generally occurs between 1 and 2 h after oral ingestion. In the post-operative setting, T_{max} is delayed up to 6 h, likely due to impaired alimentary motility, but the area under the curve (AUC) was not significantly altered. Hence, the total amount of drug absorbed was not significantly affected. Concomitant administration of food did not affect absorption [35].

3.2. Rivaroxaban

Rivaroxaban has a half-life of 7–8 h and is usually administered once daily. Rivaroxaban should be held to allow at least 48 h to elapse between the last dose of drug and surgery. This is consistent with manufacturer recommendations to hold the dose the day prior to surgery [33]. Reinitiation of rivaroxaban can occur once hemostasis is achieved, and T_{max} occurs roughly 2 h after oral ingestion.

3.3. Apixaban

Apixaban's half-life is 11 h, requiring a total of 55 h to clear from the body. Manufacturer suggests holding the drug 1–2 days before the anticipated procedure (2 days if very high risk of bleeding). As apixaban is given twice daily, this will allow 36–60 h to elapse between the last dose and time of procedure [32]. Theoretically, <12.5% of C_{max} will exist in the body at 36 h, making the extent of anticoagulation clinically insignificant for a procedure without high bleeding risk. Apixaban can be reinitiated once hemostasis is achieved, and T_{max} occurs ~2–3 h after oral ingestion. A fed or fasted state did not affect T_{max} [24].

Table 2
Recommended time to interrupt NOACs from last dose to anticipated procedure based on renal function.

Renal function		Dabigatran	Rivaroxaban	Apixaban	Edoxaban
CrCl >80 mL/min	Moderate bleeding risk	1 day	1 day	1 day	1 day
	High bleeding risk	2 days		2 days	
CrCl 50–80 mL/min		3 days	1 day	2 days	2 days
CrCl 30–50 mL/min		4 days	1 day	3 days	3 days
CrCl 15–30 mL/min		5 days	2 days	N/A	3 days

CrCl — creatinine clearance.

3.4. Edoxaban

Edoxaban is dosed once daily, has a half-life of 9 h, and can be stopped the day before anticipated surgery, allowing 48 h to elapse between the last dose and time of procedure. This is consistent with manufacturer recommendations [12]. Reinitiation of edoxaban should occur once hemostasis is achieved, and T_{max} occurs roughly 1–2 h after oral ingestion (Table 1).

4. Renal impairment

Renal excretion of unchanged drug plays a critical role in NOAC clearance, can increase bleeding risk and impacts periprocedural interruption of anticoagulation. The apparent clearance of the drug decreases with the extent of renal impairment for all 4 NOACs [11,36–38]. Dabigatran exhibited significant delays in drug clearance with worsening renal function (Table 1). With the CrCl less than 30 mL/min, half-life doubled from 14 to 28 h [38]. In addition, total drug exposure increased by >6 fold when compared to healthy controls with aPTT increasing 1.9–3.5 times normal with severe renal impairment [38]. In patients undergoing elective total hip replacement, a CrCl <40 mL/min doubled the plasma concentration of dabigatran compared to those with normal CrCl [39]. When the CrCl is <30 mL/min, dabigatran should be stopped at least 5 days prior to anticipated procedure. In this situation, it may be advisable to consider bridging with parenteral anticoagulation. Fortunately, hemodialysis removes 62–68% of dabigatran in patients with ESRD, and can be considered in those with severe renal impairment and requiring urgent surgical intervention [38].

Rivaroxaban also exhibits delay in clearance with renal impairment, but not to the same extent as dabigatran. In a study of 758 patients undergoing elective total hip replacement on rivaroxaban, a CrCl <30 mL/min resulted in ~17% higher drug exposure [40]. Factor Xa inhibition was 1.5 times when CrCl was between 50 and 80 mL/min, 1.86 times higher with CrCl between 30 and 50 mL/min, and 2 fold higher when CrCl was <30 mL/min [36]. Although half-life is not prolonged significantly with CrCl <30 mL/min, given increased drug exposure, it is prudent to stop rivaroxaban at least 48 h prior to anticipated procedure. Dialysis does not effectively remove rivaroxaban [41].

Renal impairment has a significant impact on apixaban clearance. The half-life rises to 14.2 h with a CrCl of 50–80 mL/min, and 18.2 h with a CrCl between 30 and 50 mL/min [37]. As such, apixaban should be held 2 days prior to anticipated procedure when the CrCl is between 50 and 80 mL/min, and 3 days prior to anticipated procedure when the CrCl is <50 mL/min. No data is available to address a CrCl <30 mL/min. Apixaban is not effectively removed by dialysis [32].

Edoxaban clearance is also significantly affected by renal excretion, with the half life increasing to 13 h when the CrCl is between 50 and 80 mL/min, to 17 h with CrCl of 30–50 mL/min, and 18 h when CrCl is <30 mL/min [11]. Our recommendation is to hold edoxaban 48 h prior to planned surgery for a CrCl between 50 and 80 mL/min, and 72 h prior to surgery when the CrCl is <50 mL/min. Edoxaban also cannot be effectively removed by dialysis [42].

Even in the setting of renal impairment, NOACs are just as safe and efficacious as warfarin [43]. However, given any degree of renal impairment, the clearance of each NOAC is reduced to a variable extent; therefore it is critical to ensure that the time of discontinuation for each agent in question is consistent with its delay in drug clearance (Table 2).

5. Hepatic impairment

With the exception of rivaroxaban, available literature suggests that NOACs are not significantly affected by mild hepatic impairment. It should be noted that most studies only included patients with liver disease categorized as Child–Pugh class A or B [44–47]. In patients with Child–Pugh class B liver disease, a single-dose of rivaroxaban showed a 2.3 fold increase in AUC, with half life increasing to 10 h along with

a 2.6 fold increase in factor Xa inhibition [45]. Though the manufacturer specifically warns against using rivaroxaban in patients with Child–Pugh class B liver disease, in the event a patient with moderate hepatic impairment is on rivaroxaban and needs surgical intervention, given these findings, it is still advisable to stop the medication 24 h before anticipated surgery.

The NOACs should not be used in patients with moderate to severe hepatic impairment due to paucity of data regarding their use in patients with intrinsic coagulation abnormalities. In patients who have developed severe hepatic impairment in the periprocedural setting, the NOAC needs to be discontinued and not reinitiated in the post-operative setting.

6. Specific procedures

6.1. Neurosurgery, spinal anesthesia, and epidural catheterization

Any type of neurosurgery, including spinal anesthesia or any procedure that accesses the epidural space, should be considered a high bleeding risk surgery in the setting of NOAC use [10]. With normal renal function, dabigatran and apixaban should be stopped at least 2 days, and rivaroxaban and edoxaban should be stopped at least 1 day in advance of these procedures (Table 2), which is also consistent with manufacturer recommendations [12,28,32,33]. The European Society of Anesthesia Guidelines recommend that the intrathecal catheter should not be removed any earlier than 34 h after the last dose of dabigatran, 26–30 h after the last dose of apixaban, and 22–26 h after the last dose of rivaroxaban [48]. Intrathecal catheters should not be removed any earlier than 12 h after the last dose of edoxaban per manufacturer recommendations [12]. After removal of the catheter, the next dose should be at least 2 h after for edoxaban, 5 h for apixaban, and 6 h for rivaroxaban [12,32,33]. Given the limited data available with regards to NOAC use and epidurals, we recommend strict adherence to manufacturer recommendations.

6.2. Orthopedic surgery

Joint arthroplasty procedures carry an increased risk of bleeding [2]. Post-operatively, an increased risk of VTE secondary to immobilization requires VTE prophylaxis. All of the NOACs available on the market have been shown to be as efficacious as LMWH in the prevention of VTE following total hip and total knee arthroplasty, and resuming respective NOACs post-operatively will offer effective VTE prevention [49–56]. The 9th American College of Chest Physicians recommends that NOACs can generally be started 12 h post-operatively [57]. However, if thromboembolism risks are prohibitively high, other experts advocate that the first dose can be as soon as 1–4 h postoperatively for dabigatran and 6–10 h postoperatively for rivaroxaban [58].

6.3. Angiography and angioplasty during acute coronary syndrome

Angioplasty, especially in the setting of acute coronary syndrome (ACS) and/or need for dual antiplatelet therapy (DAPT), presents many challenges to the physician taking care of patients on NOACs as available data is limited. Heidbuchel et al. consider angiography to be an intermediate risk procedure, and recommend NOACs be stopped 24 h before elective angiography [10]. However, in the setting of ACS, there is overwhelming evidence suggesting increased bleeding events when NOACs are combined with DAPT [59–61]. Rivaroxaban has the most evidence, where small doses less than those used for AF prophylaxis or VTE treatment resulted in significant bleeding even after stabilization of ACS [62]. In the setting of ACS and possible angioplasty, we recommend NOACs be discontinued, which is consistent with previously published recommendations [63]. Anticoagulation with either UFH or LMWH may be initiated as part of standard ACS treatment when the next dose of NOAC is due. In non-emergent ACS cases, angiography/angioplasty should take place at the next dosing interval when the drug concentration is at its trough. Once sheaths are removed, NOACs can be restarted in 4–6 h if there is no evidence of significant bleeding.

If patients require DAPT post-procedurally, the combination of VKA and clopidogrel is a safe and efficacious alternative over anticoagulation in addition to DAPT [64,65]. The risk-benefit ratio of using NOACs in this setting is limited and not well-studied [66]. Therefore, the bleeding risk in each individual case should be carefully considered before the NOAC is reinitiated or switched to a VKA and clopidogrel if bleeding risks are significant.

6.4. Pacemaker and implantable cardioverter defibrillator implantation

While there is much data surrounding the periprocedural use of warfarin for permanent pacemaker (PPM)/ implantable cardioverter defibrillator (ICD) implantation, data on NOAC use in this setting are limited [67–71]. Recent surveys of high-volume device placement centers suggest that the clinical practice is to interrupt NOAC therapy prior to pacemaker and ICD implantation [72]. Recent evidence suggests that the risk of pocket hematomas is 2–3% with uninterrupted oral anticoagulation [68]. A recent study suggests that the use of NOACs during PPM/ ICD placement confers an intermediate risk of bleeding [69]. Given paucity of data available for NOAC use in this setting, it is reasonable to interrupt NOAC therapy prior to device implant based on recommendations provided in Table 2.

With regard to bridging, multiple studies, including a prospective randomized trial as well as a meta-analysis have demonstrated that uninterrupted warfarin therapy results in significantly less pocket hematomas versus bridging with heparinoids [67,70,73,74].

In light of these studies, it appears that the risks of bridging outweighs the benefits during device placement, especially considering the short period of unprotected time given the rapid clearance of NOACs. Further studies are needed on the subject of uninterrupted NOAC use during pacemaker and ICD implantation. Until then, it is prudent to stop NOAC therapy prior to device placement for the recommended period without bridging.

6.5. Catheter ablation of AF

Catheter ablation for AF distinguishes itself from all other procedures discussed previously in that the thombogenic risks of this procedure may greatly outweigh the risk of bleeding. Guidelines currently recommend that patients receive therapeutic anticoagulation for at least 3 weeks prior to AF ablation, but do not specify whether bridging is required [75]. A meta-analysis demonstrated that AF ablation in the setting of uninterrupted therapeutic warfarin throughout the periprocedural period resulted in less thrombotic events and comparable bleeding rates when compared to individuals who had discontinuation of warfarin and heparin bridging [76]. Additionally, a randomized prospective trial of 1584 patients confirmed that an uninterrupted warfarin approach in the periprocedural setting for AF ablation resulted in significantly less thromboembolic events [77]. Furthermore, use of diffusion MRI revealed a disturbing number ($n = 50$) of "silent cerebral ischemia" events in a small cohort of 86 patients who underwent AF ablation, and a multicenter study showed that tight control of INR reduces the incidence of silent cerebral ischemia [78,79]. Though all of these patients were asymptomatic from their strokes, this finding places the risk/benefit ratio clearly in favor of continued oral anticoagulation in these patients. In summary, uninterrupted periprocedural anticoagulation for AF ablation has essentially become the gold-standard.

Dabigatran, rivaroxaban, and apixaban have all been studied in the periprocedural setting for AF ablation. Single-center studies have shown that dabigatran, both uninterrupted and held 24 h prior to procedure, resulted in no significant bleeding or thromboembolic events compared to uninterrupted warfarin prior to catheter AF ablation [80,81]. However, a prospective, multi-center observational study

comparing uninterrupted dabigatran to uninterrupted warfarin demonstrated both increased bleeding and thromboembolic complications in the dabigatran arm [82]. Furthermore, a meta-analysis of 5500 patients also showed that dabigatran use prior to catheter AF ablation had more thromboembolic events compared to warfarin with similar bleeding events [83]. Intra-operatively, more heparin was required to maintain adequate activated clotting time levels in patients receiving dabigatran [84]. Thus, while there is much data comparing dabigatran to warfarin, the evidence is unclear as to whether dabigatran should be used in this setting.

Studies involving other NOACs in this setting are also available, but less numerous. Studies comparing uninterrupted rivaroxaban to uninterrupted warfarin during AF ablation demonstrated no significant difference in the rates of bleeding or thromboembolic events [85–87]. Similar studies involving apixaban have also showed no differences between uninterrupted apixaban and warfarin [88,89]. In one particular study, diffusion MRI was also performed on 29 patients in the apixaban arm and revealed no silent cerebral ischemia events. A recent analysis of 374 patients in the ORBIT-AF registry undergoing AF ablation using either dabigatran, rivaroxaban, and apixaban during the periprocedural period versus warfarin demonstrated less bleeding with dabigatran only [90]. There was no difference in thromboembolic rates between any of the drugs. Post-procedure, current guidelines recommend restarting oral anticoagulation 4–6 h after sheaths are removed [91].

Currently, there is early evidence to suggest that NOACs are as safe as warfarin for periprocedural catheter ablation of AF [87]. However, further studies are required and 2 large, randomized prospective trials, one comparing dabigatran (RE-CIRCUIT) and the other comparing apixaban (AXAFA — NCT02227550) to warfarin in this setting, are underway and may help answer this question [92]. However, given the lopsided risk/benefit in favor of maintaining anticoagulation during AF ablation, when NOACs are used, we recommend no interruption of the regimen prior to the procedure.

6.6. Reversal of NOAC

Although there is no FDA-approved reversal agents for NOAC, several strategies have been investigated and proposed to reverse or decrease the anticoagulation effect in case of life-threatening bleeding or in emergent periprocedural setting [93].

Activated charcoal was shown to be effective in limited studies if dabigatran was ingested within 1–2 h [27,93,94]. Only few reports suggested clinical benefit of prothrombin complex concentrate (PCC), recombinant activated VIIa (rFVIIa) or anti-inhibitor coagulant complex for dabigatran reversal in the setting of life-threatening bleeding [95–97], whereas some other reports did not confirm such benefit [93,98,99].

For factor Xa inhibitors, activated charcoal within 1–2 h of ingestion can be used to limit their effect, but not hemodialysis [93]. Four-factor PCC and rFVII has shown to be effective in reducing bleeding times caused by rivaroxaban [98,100–102]. Recently, a novel recombinant human factor Xa, andexanet alfa (AnXa) that binds with high affinity to apixaban and rivaroxaban has showed promising results in phase 3 studies [103,104]. However, AnXa is currently not commercially available. Thus, if criteria for activated charcoal or hemodialysis use are not met, the use of four-factor PCC (25 U/kg, maximum dose of 2500 U) may be attempted to reverse dabigatran, as well as rivaroxaban and apixaban [93].

7. Conclusions

The use of NOACs for stroke prophylaxis in AF and treatment of VTE is becoming more and more prevalent. However, available data assessing efficacy and safety of periprocedural NOAC use is limited and not as abundant as the data for warfarin. Therefore, it is somewhat challenging to provide specific recommendations as it relates to NOACs in this setting. However, predictable pharmacokinetics, rapid rate of elimination, and quick onset of action provide NOACs with a distinct pharmacokinetic advantage over warfarin and may make them safer agents to use in this setting. On the other hand, NOACs suffer from lack of a universally effective reversal agent which creates challenges if a major periprocedural bleed were to occur. While we await better data and evidence, a firm grasp and awareness of these advantages and disadvantages in relation to the thromboembolic and bleeding risk of the patient can lead to safer and more efficacious decision-making.

Author contributions

P.L. Mar and R. Gopinathannair contributed to the conceptualization of this study. P.L. Mar and D. Familstev contributed to the drafting of the manuscript with substantial revisions made by R. Gopinathannair, M.D. Ezekowitz and D. Lakkireddy. All authors revised the article critically for intellectual content and all approved the final article.

Conflict of interests

P.L. Mar and D. Familstev have no conflict of interests to declare. M.D. Ezekowtiz is a consultant and speaker for Boehringer Ingelheim, Pfizer, Sanofi Aventis, Bristol–Myers Squibb, Portola, Daiichi Sankyo, Medtronic, Aegerion, Merck, Johnson & Johnson, Gilead Sciences, Inc., Janssen, Pozen Inc., and Coherex Medical. D. Lakkireddy is a consultant and speaker for Janssen, Pfizer, Biosense Webster, SentreHEART, and St. Jude Medical. R. Gopinathannair is a consultant and speaker for St. Jude Medical, Abiomed, Pfizer, and Bristol–Myers Squibb.

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