AHA SCIENTIFIC STATEMENT

Management of Patients on Non–Vitamin K Antagonist Oral Anticoagulants in the Acute Care and Periprocedural Setting

A Scientific Statement From the American Heart Association

ABSTRACT: Non–vitamin K oral anticoagulants (NOACs) are now widely used as alternatives to warfarin for stroke prevention in atrial fibrillation and management of venous thromboembolism. In clinical practice, there is still widespread uncertainty on how to manage patients on NOACs who bleed or who are at risk for bleeding. Clinical trial data related to NOAC reversal for bleeding and perioperative management are sparse, and recommendations are largely derived from expert opinion. Knowledge of time of last ingestion of the NOAC and renal function is critical to managing these patients given that laboratory measurement is challenging because of the lack of commercially available assays in the United States. Idarucizumab is available as an antidote to rapidly reverse the effects of dabigatran. At present, there is no specific antidote available in the United States for the oral factor Xa inhibitors. Prothrombin concentrate may be considered in life-threatening bleeding. Healthcare institutions should adopt a NOAC reversal and perioperative management protocol developed with multidisciplinary input.

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As the US population ages, the burden of atrial fibrillation (AF) and venous thromboembolic disease is expected to increase, and prescriptions for long-term anticoagulation will climb. Anticoagulated patients are vulnerable to spontaneous, traumatic and perioperative bleeding. Warfarin is a vitamin K antagonist (VKA) that has been used for decades to prevent and treat arterial and venous thromboembolism (VTE). More recently, 4 non–vitamin K antagonist oral anticoagulants (NOACs) have been approved in the United States as alternatives to warfarin for prevention of stroke resulting from nonvalvular AF (NVAF), and prevention and treatment of VTE. These are dabigatran etexilate (Pradaxa, Boehringer Ingelheim, Germany); rivaroxaban (Xarelto, Bayer HealthCare AG, Leverkusen, Germany), apixaban (Eliquis, Pfizer and Bristol-Myers Squibb, New York, NY) and edoxaban (Savaysa, Daiichi Sankyo, Tokyo, Japan). Direct oral anticoagulants has been proposed as alternative nomenclature for these class of agents.[1] NOACs are associated with comparable or lower risk of stroke, systemic embolism, major bleeding, and death compared with warfarin for NVAF.[2–5] In contrast with warfarin, NOACs have a more predictable therapeutic effect, do not require routine monitoring, have fewer potential drug-drug interactions and no restriction on dietary consumption of vitamin K–containing food. However, universal adoption of NOACs has been stunted by the lack of specific antidotes and measurement assays. This scientific statement reviews the literature and offers practical suggestions for providers who manage patients who are actively bleeding and who are at risk for bleeding in the acute care and periprocedural setting. This statement focuses on interpreting available data rather than providing specific man-

Key Words: AHA Scientific Statements ■ acute care ■ anticoagulants ■ non–vitamin K antagonist ■ periprocedural

agement recommendations in under-studied populations such as oncology patients.

Members of this American Heart Association (AHA) writing group were selected for their diverse expertise in cardiovascular medicine, emergency medicine, critical care, neurology, surgery, and pharmacology. A systematic search of the literature for each subtopic was performed in PubMed and Ovid and was supplemented by review of bibliographies as well as manual searches of key articles. Each of the following search terms were included individually and in combination: *dabigatran*, *apixaban*, *rivaroxaban*, *edoxaban*, *anticoagulation*, *reversal*, *antidote*, *atrial fibrillation*, *venous thromboembolism*, *bleeding*, *intracranial*, *cardioversion*, *catheterization*, *cardiac implantable devices*, *kidney injury*, *transition*, *switching*, *pharmacology*, *andexanet alfa*, *idarucizumab*, *ciraparantag*, *gastrointestinal, trauma, surgery, percutaneous coronary intervention*, *neuraxial anesthesia*, *stroke*, and *overdose*. Writing group members were instructed to write subtopic sections aligned with their experience. Members were instructed to cite contemporary guidelines and scientific statements where appropriate. The writing group did not assign formal classes of recommendation/level of evidence per the AHA Scientific Document Development Process recommendation that went into effect September 1, 2015. Sections were then reviewed by another writing group member. Section drafts were submitted to the writing group chair and co-chair and compiled into a single document. Web and teleconferences were convened to review and edit the full draft. The final document was submitted for independent peer review and approved for publication by the AHA Manuscript Oversight Committee on April 29, 2016.

PHARMACOLOGY OF NOACS

NOACs act through direct inhibition of thrombin or inhibition of factor Xa (Figure 1). Dabigatran etexilate mesylate is a competitive direct thrombin inhibitor. Rivaroxaban, apixaban, and edoxaban inhibit factor Xa and prothrombinase activity, thus inhibiting the conversion of prothrombin to thrombin. Thrombin catalyzes the conversion of fibrinogen to fibrin; activates factors V, VIII, XI, and XIII; and activates platelets. Therefore, inhibiting thrombin decreases thrombus formation. In contrast with warfarin, NOACs have a rapid onset of action, a shorter half-life, and more predictable pharmacokinetics. Routine therapeutic monitoring was not done in the major NOAC efficacy trials and is at present not recommended in usual clinical practice. Information pertaining to NOAC dose, time to peak effect, and time to offset of effect is outlined in Table 1.

NOACs are substrates for P-glycoprotein (P-gp) transport and apixaban and rivaroxaban are substrates for CYP 3A4 metabolism. Therefore, concomitant medications that are inducers or inhibitors of these pathways should be evaluated for the potential to interact (Table 2). Macrolides and nondihydropyridine calcium channel blockers are 2 commonly prescribed classes of medications that impact therapeutic levels of NOACs, although a post hoc analysis of ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) showed no evidence of differential outcomes between rivaroxaban and warfarin in patients treated with ≥1 combined P-gp and CYP 3A4 inhibitors.[6] Edoxaban exists in a predominantly unchanged form

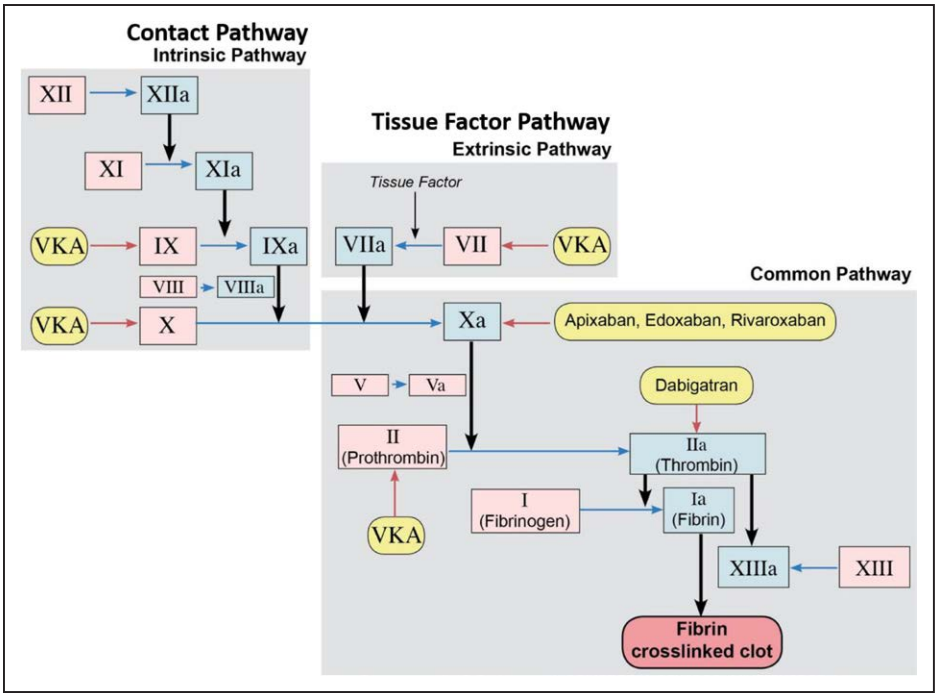

Figure 1. Clotting cascade and anticoagulants.
VKA indicates vitamin K antagonist.

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Table 1. Comparison Among NOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Approved indications	Nonvalular AF ↓ Risk of stroke and systemic embolism	Nonvalular AF ↓ Risk of stroke and systemic embolism	Nonvalular AF ↓ Risk of stroke and systemic embolism	Nonvalular AF ↓ Risk of stroke and systemic embolism. Limitation: should not use in patients with CrCl >95 mL/min as a result of ↑ risk of ischemic stroke compared with warfarin at 60 mg
	DVT, PE Treatment after 5–10 d parenteral AC ↓ Recurrence Prophylaxis after hip replacement	DVT, PE Treatment ↓ Recurrence Prophylaxis after hip or knee replacement	DVT, PE Treatment ↓ Recurrence Prophylaxis after hip replacement	DVT, PE ↓ Recurrence Treatment after 5–10 d initial parenteral AC
Mechanism of action	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Time to peak	1 h; delayed to 2 h with food	2–4 h	3–4 h	1–2 h
Bioavailability	3%–7%	10-mg dose: 80%–100% 20-mg dose: 66% ↑ With food	~50%	62%
Plasma protein binding	35%	92%–95%	~87%	55%
Volume of distribution	50–70 L	50 L	21 L	107 L
Plasma $t_{1/2}$	12–17 h Elderly 14–17 h Mild to moderate renal impairment 15–18 h Severe renal impairment 28 h	5–9 h Elderly 11–13 h	~12 h (8–15 h)	10–14 h
Metabolism	Hepatic and plasma hydrolysis to active dabigatran	Hepatic: oxidation by CYP3A4/5, CYP2J2; hydrolysis to inactive metabolites (51%)	Hepatic: 25% mainly by CYP3A4/5; lesser by CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2J2; O-demethylation and hydroxylation	Minimal CYP3A4 hydrolysis, conjugation, oxidation
	Hepatic glucuronidation to active metabolites (<10%)	P-gp substrate	No active circulating metabolites	Active metabolite (M-4, <10% of parent)
	P-gp substrate	No major or active circulating metabolites	Substrate of CYP3A4, P-gp, BCRP	P-gp substrate
		Substrate of P-gp and ABCG2 (BCRP)		
Excretion	Renal (~80%) after IV administration	Renal (66%): 36% active, 30% inactive metabolites	Renal (27%)	Renal (~50%): primarily as unchanged drug
	After oral, 7% recovered in urine, 86% in feces	Feces (28%): 7% active, 21% inactive metabolites	Biliary and direct intestinal excretion	Metabolism and biliary/intestinal excretion accounts for the rest

(*Continued*)

Table 1. Continued

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dosing				
Nonvalvular AF	CrCl >30 mL/min: 150 mg BID	CrCl >50 mL/min: 20 mg daily with evening meal	5 mg BID	CrCl >50 to ≤95 mL/min: 60 mg daily
	CrCl 15–30 mL/min: 75 mg BID	CrCl 15–50 mL/min: 15 mg daily with evening meal	2.5 mg BID, if 2 of 3 characteristics: Cr ≥1.5 mg/dL, age ≥80 y, weight ≤60 kg	CrCl 15–50 mL/min: 30 mg daily
	CrCl <15 mL/min or on dialysis: Not recommended	Not recommended for CrCl <15 mL/min or on dialysis in patients with AF		NOT recommended for CrCl >95 mL/min
	CrCl 30–50 mL/min with concomitant P-gp inhibitors: 75 mg BID			
	CrCl <30 mL/min with concomitant P-gp inhibitors: Avoid coadministration			
DVT or PE treatment	CrCl >30 mL/min: 150 mg BID after 5-10 d parenteral anticoagulation	15 mg BID with food first 21 d for initial treatment, then 20 mg once daily with food	10 mg BID x 7 d, then 5 mg BID	60 mg once daily
	CrCl ≤30 mL/min or on dialysis: Not recommended	Not recommended for CrCl <30 mL/min in patients with DVT or PE		CrCl 15–50 mL/min or weight ≤60 kg or on certain P-gp inhibitors: 30 mg once daily
↓ in recurrent DVT/PE	CrCl >30 mL/min: 150 mg BID after 5–10 d parenteral anticoagulation	20 mg daily with food	2.5 mg BID	
	CrCl ≤30 mL/min or on dialysis: Not recommended			
DVT, PE prophylaxis after hip or knee replacement	After hip replacement surgery: CrCl >30 mL/min after achievement of hemostasis: If given day of surgery, 110 mg 1–4 h postop; after day of surgery 220 mg once daily x 28–35 d CrCl ≤30 mL/min or on dialysis: Not recommended CrCl <50 mL/min with concomitant P-gp inhibitors: Avoid coadministration	Initial dose 6–10 h after surgery provided hemostasis established 10 mg daily with or without food x 35 d for hip replacement, x 12 d for knee replacement	2.5 mg BID x 35 d after hip replacement surgery or x 12 d after knee replacement surgery	
Additional dosing comments		Avoid use with patients with moderate-severe hepatic impairment (Child-Pugh class B/C) or hepatic disease with coagulopathy	Not recommended in patients with severe hepatic impairment (Child-Pugh class C)	Not recommended with CrCl <15 mL/min
		15-20 mg taken with food; 10 mg with or without food		Not recommended in patients with moderate-severe hepatic impairment (Child-Pugh class B/C)

(*Continued*)

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Table 1. Continued

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Therapeutic measurement	Routine not required	Routine not required	Routine not required	Routine not required
	To detect presence: aPTT, ECT (if available), TT	To detect presence: PT, aPTT, antifactor Xa activity	To detect presence: PT, aPTT, antifactor Xa activity	Prolongs PT, aPTT, antifactor Xa activity
	aPTT >2.5 times control may indicate overanticoagulation	Renal function, CBC periodically, at least annually; hepatic function	Renal function, CBC periodically, at least annually	Renal function, CBC periodically, at least annually
	Renal function, CBC periodically, at least annually			

AC indicates anticoagulant; AF, atrial fibrillation; aPTT, activated partial thromboplastin time; BID, twice daily; CBC, complete blood count; CrCl, creatinine clearance; DVT, deep vein thrombosis; ECT, ecarin clotting time; IV, intravenous; NOACs, non–vitamin K antagonist oral anticoagulants; PE, pulmonary embolism; P-gp, P-glycoprotein; PT, prothrombin time; and TT, thrombin time.

in plasma with minimal metabolism through hydrolysis, conjugation, and oxidation by CYP 3A4.

LABORATORY MEASUREMENT OF NOAC EFFECT

One advantage of NOACs over warfarin is more rapid onset and offset of action with predictable pharmacokinetics and anticoagulant effect. This eliminates the necessity for routine therapeutic monitoring except for periodic assessment of renal function.[7] Laboratory measurement of NOAC level or effect may be necessary in certain acute care or perioperative settings, particularly when there is uncertainty about the timing of last ingestion, renal function, and gastrointestinal absorption. However, the lack of US Food and Drug Administration–approved NOAC laboratory assays complicates the management of NOAC overdose, NOAC-associated life-threatening bleeding, and the scheduling of urgent surgical procedures.[8] All NOAC agents affect routine coagulation tests but not in a manner that allows for a predictable and quantitative measurement of anticoagulation effect. Specific NOAC agents are subsequently discussed.

Dabigatran

This agent is known to prolong the activated partial thromboplastin time, prothrombin time, and thrombin time. The package insert recommends using partial thromboplastin time for measurement; however, there is no defined partial thromboplastin time therapeutic range for dabigatran and the assay is relatively insensitive to different plasma concentrations of direct thrombin inhibitors. Furthermore, the partial thromboplastin time cannot be used in patients with lupus anticoagulant or an intrinsic clotting factor deficiency because its prolongation from these conditions would mask the anticoagulant effect of dabigatran. Thrombin time is far more sensitive, and prothrombin time is less sensitive to dabigatran. A normal partial thromboplastin time or thrombin time most likely excludes therapeutic levels of dabigatran, whereas a normal prothrombin time may not. Quantitative assessments of dabigatran levels can be obtained with the dilute thrombin time, the ecarin clotting time, or the ecarin chromogenic assay. Thrombin time and ecarin-based assays show excellent linearity across on-therapy drug concentrations and may be used for drug quantification. However, the US Food and Drug Administration has not approved these latter assays for measuring levels of dabigatran or other direct thrombin inhibitors.[8]

Rivaroxaban, Apixaban, Edoxaban

At present, there are no US Food and Drug Administration–approved assays or calibration reagents to measure the effect of direct oral factor Xa inhibitors. Rivaroxaban and apixaban affect activated clotting time and chromogenic anti–factor Xa assay; however, no therapeutic range exists. Prothrombin time is less sensitive (especially for apixaban), and a normal prothrombin time may not exclude clinically relevant levels. Partial thromboplastin time demonstrates insufficient sensitivity and linearity for quantification.[9] Studies using spiked plasma samples suggest using prothrombin time for a qualitative assessment of direct oral factor Xa inhibitors or chromogenic anti–factor Xa assay for a quantitative assessment of direct oral factor Xa inhibitors.[8–10] Anti-Xa activity is linear over a wide range of drug levels and may be used for drug quantification. Undetectable anti-Xa activity likely excludes clinically relevant drug concentrations.

In summary, although routine NOAC monitoring is unnecessary, measurement of NOAC effect may assist clinical management in certain acute care and periprocedural settings. In most situations, the time of last drug ingestion combined with a recent assessment of creatinine clearance (CrCl) should enable appropriate clinical decision making.

Table 2. NOAC Drug Interactions

NOAC	Interacting Medications	Effect on NOAC	Labeled Guidance; Comments
Dabigatran	P-gp inducer: rifampin	↓ Dabigatran exposure	Concomitant use should generally be avoided.
	P-gp inhibitors: ketoconazole, dronedarone	↑ Dabigatran exposure if concomitant moderate renal impairment	If moderate renal impairment (CrCl 30–50 mL/min) ↓ to 75 mg BID during concomitant use
	P-gp inhibitors: ketoconazole, dronedarone, verapamil, amiodarone, quinidine, clarithromycin, ticagrelor	↑ Dabigatran exposure if concomitant severe renal impairment	If severe renal impairment (CrCl 15–30 mL/min) avoid concomitant use
Apixaban	Strong dual P-gp and CYP3A4 inducers: rifampin, carbamazepine, phenytoin, St. John's wort	↓ Apixaban exposure	Avoid concomitant use
	Strong dual P-gp and CYP3A4 inhibitors: ketoconazole, itraconazole, ritonavir, clarithromycin	↑ Apixaban exposure	In patients on 5 mg or 10 mg BID, ↓ dose by 50% when coadministered
			Avoid coadministration on 2.5 mg BID
Rivaroxaban	Combined P-gp and strong CYP3A4 inducers: rifampin, carbamazepine, phenytoin, St. John's wort	↓ Rivaroxaban exposure	Avoid concomitant use; may decrease rivaroxaban efficacy
	Combined P-gp and strong CYP3A4 inhibitors: ketoconazole, itraconazole, HIV protease inhibitors (ritonavir, lopinavir/ritonavir, indinavir), conivaptan	↓ Rivaroxaban exposure	Avoid concomitant use
	Combined P-gp and moderate CYP3A4 inhibitors: diltiazem, verapamil, amiodarone, dronedarone, erythromycin	↑ Rivaroxaban exposure in patients with renal impairment	In patients with CrCl 15 to <80 mL/min, rivaroxaban should not be used concomitantly unless the potential benefit justifies the potential risks
			No evidence of interaction observed in ROCKET AF between treatment assignment and outcomes in patients using ≥1 combined P-gp and moderate 3A4 inhibitors (including amiodarone, diltiazem, and verapamil)[6]
Edoxaban	P-gp inducer: rifampin	↓ Edoxaban exposure	Avoid concomitant use
	Strong P-gp inhibitors: ritonavir, nelfinavir, saquinavir, indinavir, cyclosporine	↑ Edoxaban exposure	Avoid concomitant use in patients taking edoxaban for treatment of VTE
	P-gp inhibitors: verapamil, quinidine, azithromycin, clarithromycin, itraconazole, ketoconazole	↑ Edoxaban exposure	↓ to 30 mg daily during concomitant administration for patients taking edoxaban for the treatment of VTE
			Dose reduction is not recommended for AF indications
			In ENGAGE AF, a ↓ dose of edoxaban as a result of concomitant P-gp inhibitor use (verapamil, quinidine, dronedarone) was associated with ↓ edoxaban exposure and a relative ↑ in risk of stroke or systemic embolism with edoxaban relative to warfarin[176]

AF, atrial fibrillation; BID, twice daily; CrCl, creatinine clearance; ENGAGE AF, Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation trial; NOAC, non–vitamin K antagonist oral anticoagulant; P-gp, P-glycoprotein; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; and VTE, venous thromboembolism.

NOAC REVERSAL

This AHA writing group suggests hospital systems adopt anticoagulation reversal protocols with multidisciplinary representation from emergency medicine, critical care, cardiology, hematology, gastroenterology, neurology, neurosurgery, trauma, acute care surgery, cardiothoracic surgery, vascular surgery, pharmacy, and nursing. An example of a NOAC reversal protocol is shown in Figure 2.

Dabigatran

For minor bleeding, supportive care and careful observation are suggested. For major bleeding, intravenous idarucizumab (Praxbind, Boehringer-Ingelheim, Germany) at a dose of 5 grams (2 consecutive intravenous infusions of 2.5 g each) will reverse the anticoagulant effect of dabigatran within minutes.[11] Idarucizumab is a monoclonal antibody fragment that binds dabigatran with an affinity 350 times that of thrombin. The RE-VERSE AD (Reversal Effects of Idarucizumab on Active Dabigatran) was a prospective cohort study that showed that idarucizumab administration reversed anticoagulation as evidenced by the normalization of the dilute thrombin time and ecarin clotting time within minutes among subjects suffering a serious hemorrhage or who required an urgent procedure.[11] Early hemostasis was achieved in bleeding subjects, and a low rate of perioperative bleeding events was observed in subjects undergoing urgent surgery. However, the strength of these clinical observations is limited by the nonrandomized nature of this study.

Several studies have investigated the efficacy of prothrombin complex concentrates (PCCs), recombinant factor VII activated, and fresh frozen plasma (FFP) in animal models; however, human data are mixed. One randomized, placebo-controlled trial in healthy men treated with dabigatran showed that 4-factor PCC did not reverse the dabigatran effect on partial thromboplastin time, endogenous thrombin potential lag time, thrombin time, or ecarin clotting time.[12] Case reports of patients with life-threatening bleeding associated with dabigatran therapy have demonstrated mixed results with the use of FFP, recombinant factor VII activated, PCCs, fibrinogen, and platelets.[8]

Hemodialysis may remove 49% to 57% of dabigatran within 4 hours given that the drug is only 35% bound to plasma proteins.[13,14] Hemodialysis may be considered if the CrCl is chronically below 30 mL/min or in acute kidney injury. For major ingestion, there is some evidence to support the use of activated charcoal therapy if dabigatran was consumed within 1 to 2 hours; however, care must be taken to prevent aspiration in patients with decreased level of consciousness.[7,8] Furthermore, activated charcoal induced vomiting could have deleterious effects by increasing intracranial pressure in patients with intracranial hemorrhage (ICH).

In summary, the AHA writing group suggests compression when possible, supportive measures, and upfront idarucizumab in the event of dabigatran-associated major bleeding.

Rivaroxaban and Apixaban

Similar to dabigatran, activated charcoal may prevent absorption of rivaroxaban and apixaban if administered

EXAMPLE of a "Serious Bleeding on NOAC PROTOCOL"

General Measures

- mechanical compression if possible
- two sites of IV access
- determine timing of last NOAC dose
- CBC, BUN, Creatinine, liver enzymes
- plasma expanders/PRBC's as necessary
- consider activated charcoal if NOAC ingestion <2hours
- notify on-call hematologist
- Refer to chart below for specific measures

NOAC	Blood tests for NOAC presence or effect	Specific Antidote	Alternative Treatments Options
Dabigatran	PTT , TT	Idarucizumab 5 grams IV (2 infusions of 2.5 grams)	4 Factor PCC *(Kcentra®)* 50 IU/kg IV Factor VIIa 90µg/kg IV every 2 hours Tranexamic acid 15-30 mg/kg IV Hemodialysis
Rivaroxaban	Anti-Factor Xa	Unavailable in the U.S.	4 Factor PCC *(Kcentra®)* 50 IU/kg IV Factor VIIa 90µg/kg IV every 2 hours Tranexamic acid 15-30 mg/kg IV
Apixaban	Anti-Factor Xa	Unavailable in the U.S.	PCC *(Kcentra®)* 50 IU/kg IV Factor VIIa 90µg/kg IV every 2 hours Tranexamic acid 15-30 mg/kg IV
Edoxaban	Anti-Factor Xa	Unavailable in the U.S.	PCC *(Kcentra®)* 50 IU/kg IV Factor VIIa 90µg/kg IV every 2 hours Tranexamic acid 15-30 mg/kg IV

TT = thrombin time, PTT = partial thromboplastin time, PCC = prothrombin complex concentrate

Figure 2. Example of a "Serious Bleeding on a NOAC" protocol. BUN indicates blood urea nitrogen; CBC, complete blood count; IU, international units; IV, intravenous; NOAC, non–vitamin K antagonist oral anticoagulants; PCC, prothrombin complex concentrate; PRBC, packed red blood cells; PTT, partial thromboplastin time; and TT, thrombin time.

within 1 to 2 hours after NOAC ingestion. Rivaroxaban and apixaban are highly bound to plasma proteins; therefore, dialysis is ineffective in clearing these drugs. Andexanet alfa is a recombinant modified human factor Xa decoy protein that serves as a specific reversal agent to neutralize the anticoagulant effects of direct and indirect factor Xa inhibitors. This drug is administered as an initial intravenous bolus followed by an infusion for up to 2 hours. A recent study revealed that andexanet alpha reversed the laboratory assessed anticoagulant activity of rivaroxaban and apixaban in older healthy individuals within minutes of administration.[15] At present, the single arm, open-label ANNEXA-4 (Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors) trial is under way to confirm the clinical benefit of this drug in patients on apixaban, rivaroxaban, edoxaban, or enoxaparin who present with an acute major hemorrhage. An interim analysis of 67 patients revealed an 89% and 93% reduction in anti–factor Xa activity for those on rivaroxaban and apixaban respectively.[16] Of the entire cohort, 47 patients were followed for clinical hemostasis. Of these, 37 (79%; 95% confidence interval [CI], 64–89) were adjudicated as having excellent or good clinical hemostasis. The dosing protocol in this study was as follows: (1) for patients who had taken apixaban, or rivaroxaban >7 hours prior, andexanet alfa was given as a bolus dose of 400 mg followed by an infusion of 480 mg over 2 hours; and (2) for patients who had enoxaparin, edoxaban, or rivaroxaban <7 hours prior or at an unknown time, the bolus dose and infusion dose amount was doubled (800-mg bolus, 960-mg infusion over 2 hours). At present, andexanet alfa is not approved in the United States or elsewhere.

A randomized placebo-controlled study of young, healthy volunteers treated with 20 mg of rivaroxaban dosed twice daily found that administration of a 4-factor PCC led to normalization of the prothrombin time and the endogenous thrombin potential.[12] In contrast, an in vitro study using human plasma obtained from healthy donors found that recombinant factor VII activated was superior to a 4-factor PCC at normalizing laboratory coagulation studies.[17] Case reports of using FFP or PCC to treat excess rivaroxaban ingestion have shown modest success in improving laboratory coagulation parameters.[18–20] However, the correction of coagulation tests by PCC, FFP, or recombinant factor VII activated does not imply the reversal of the clinical anticoagulation effect of the drug. There is no evidence that FFP or PCC controls NOAC-associated bleeding in humans.

Edoxaban

Four-factor PCC showed dose-dependent reversal of edoxaban effect with complete reversal of bleeding duration after skin punch biopsy in volunteers and partial reversal of prothrombin time after a 50-IU/kg dose administration.[21] However, the clinical relevance of this finding is uncertain.

Ciraparantag (PER977) is a small synthetic, water-soluble, cationic molecule designed to specifically bind to unfractionated heparin and low-molecular-weight heparin through noncovalent hydrogen bonding and charge-charge interactions. It also binds in a similar way to direct Xa inhibitors and direct thrombin inhibitors. It has been shown to normalize whole blood clot time within 10 to 30 minutes of administration.[22,23] Ciraparantag is still being investigated in early clinical trials as an antidote for edoxaban associated bleeding. It remains unknown whether andexanet alfa will have greater, equal, or lesser clinical efficacy for edoxaban reversal compared with ciraparantag.

MANAGEMENT OF LIFE-THREATENING BLEEDING

All patients with life-threatening bleeding should be managed with similar basic resuscitation principals, irrespective of what type of anticoagulant they may be on. Immediate management of the patient's airway, breathing, and circulation with attempts to control hemorrhage is vital. When life-threatening bleeding occurs in a compressible area of the body, direct pressure along with selective use of tourniquets can be life-saving. Similarly, immediate resuscitation and stabilization with intravenous fluids, packed red blood cells and plasma may be required in the unstable patient. NOAC reversal as indicated in NOAC Reversal should be considered. These concepts apply to blunt and penetrating trauma, massive gastrointestinal, retroperitoneal, pericardial hemorrhage, and other forms of major bleeding.

Specific Scenario: ICH

A meta-analysis of studies that have tested NOACs for ischemic stroke prevention in NVAF have estimated a pooled incidence of hemorrhagic stroke of 0.4%.[2–5,24] Overall, this represents a >50% relative reduction in ICH rate from the 0.9% observed with warfarin. Past VKA studies suggest that ICH is 11 times more likely to result in mortality compared with extracranial hemorrhage.[25] The reduction in ICH rate coupled with consistent noninferiority compared with VKAs in preventing thrombotic events has produced a steady increase in the use of NOACs to prevent stroke in patients with NVAF.

Uniform recommendations do not exist regarding management of patients on NOACs who suffer ICH primarily because no consistent approach to their management was undertaken in the NOAC trials. Factors to consider include availability of reversal agents, the timing of urgent neurosurgery, risk of thromboembolic events during the period off

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the anticoagulant, and reinstitution of anticoagulant therapy after the ICH event or after surgery. The presence of ICH creates a unique circumstance because of the noncompressible location of the hemorrhage and poor tolerance of the brain to continued bleeding. The AHA/American Stroke Association "Guidelines for the Management of Spontaneous Intracerebral Hemorrhage" recommends prompt creation of a hemostatic environment to limit extension of the hemorrhage and before surgical treatment.[26]

Any acute neurological change in a patient on NOAC therapy should be presumed to be vascular in origin. A baseline severity score should be performed as part of the initial evaluation.[26,27] Computed tomography (CT) is widely available, detects acute hemorrhage with high sensitivity, and defines the extent of the injury on the surrounding parenchyma. Contrast-enhanced CT may identify patients at high risk of ICH expansion on the basis of the presence of contrast within the hematoma, also known as the *spot sign*.[28,29] Detailed vascular imaging may identify predisposing vascular lesions such as aneurysm, arteriovenous malformation, and dural fistula.

Concurrent with reversing the NOAC effect, blood pressure needs to be intensively managed. Many studies associate elevated systolic blood pressure with greater hematoma expansion, neurological deterioration, and death and dependency after ICH.[30,31] The INTERACT2 trial (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2) showed that acute blood pressure reduction to <140 mm Hg systolic was safe and resulted in a trend toward improvement in functional recovery despite no significant reduction in the rate of hematoma growth.[32] No patients with NOAC use were included in this trial. However, recent results from ATACH-2 (Antihypertensive Treatment of Acute Cerebral Hemorrhage-II) suggest aggressive lowering of systolic blood pressure to 110 to 139 mm Hg may not confer benefit.[32a]

The safety of resuming a NOAC regimen after ICH is a common clinical dilemma. Decisions about whether to resume anticoagulation after ICH must take into account the patient's underlying thromboembolic risk and the risk for ICH recurrence. Embolic stroke risk versus bleeding risk stratification schemes such as the CHA_2DS_2-VASc and HAS-BLED scores may help guide treatment after ICH.[30,31] The HAS-BLED score has been validated in a wide range of patients (AF and non-AF, VKA and non-VKA) and is the only bleeding risk scheme that is predictive of ICH.[33] However, a high HAS-BLED score should not be the sole consideration in clinical management. The presence of a recent ICH should prompt closer evaluation of other factors related to ICH reoccurrence.[24,34,35] Factors that are suggested to increase ICH risk include older age, poor blood pressure control, lobar ICH location, presence of microbleeds on gradient echo magnetic resonance imaging, concurrent aspirin use, and the presence of apolipoprotein E ε2 or ε4 alleles. AHA/American Stroke Association guidelines provide a class IIb recommendation for anticoagulation to be considered only after nonlobar ICH; however, this recommendation is based on warfarin-associated ICH data.[34] Whether NOACs can be safely administered in this population is still unknown.

There is no clinical trial evidence to guide the management of patients with traumatic brain injury while on anticoagulants. An initial head CT is typical; however, the role of repeated CT or inpatient observation with neurological assessment remains controversial when the initial head CT is negative. Until further data become available, NOAC reversal for traumatic ICH should be considered similar to nontraumatic ICH.

In summary, the AHA writing group suggests that traumatic and nontraumatic ICH patients on dabigatran who require NOAC reversal receive idarucizumab. ICH patients on rivaroxaban, apixaban, or edoxaban should receive PCC until more specific antidotes become available.

Specific Scenario: Trauma

The prevalence of NOAC use in the trauma population is unknown. To compare, the prevalence of warfarin use in the trauma population in 2006 was 4% with a 1.7% absolute rate increase over the previous 4 years.[36] Patients should be encouraged to carry information cards or bracelets that would alert emergency medical providers regarding oral anticoagulation use.

Apart from a few case reports, there are limited data to guide the management of NOACs in the setting of trauma.[37–42] The American College of Surgeons Advance Trauma Life Support course[43] recommends obtaining a brief, focused history during the initial evaluation of traumatically injured patients. This should include identifying the specific NOAC, timing of last ingestion, and the underlying reason for NOAC use. Laboratory testing of renal function and coagulation parameters described in Laboratory Measurement of NOAC Effect may help with treatment decisions. Thromboelastography and rotational thromboelastometry to detect NOAC activity in isolated trauma cases has been reported; however, routine use cannot be recommended until further data becomes available.[44,45]

NOACs may be held during the period of clinic assessment or until hemostasis has been achieved in trauma patients without bleeding and with mild bleeding, or bleeding from easily controllable foci. Maintaining adequate urine output and specific NOAC reversal strategies (NOAC reversal) should be considered in trauma patients with moderate or severe bleeding, or suspected bleeding that requires further evaluation.

Specific Scenario: Gastrointestinal Bleeding

In major trials, dabigatran 150 mg twice daily, rivaroxaban, and edoxaban 60 mg once daily were associated with a 1.5-fold increased risk of gastrointestinal bleeding

compared with warfarin; apixaban and dabigatran 110 mg twice daily had similar gastrointestinal bleeding risk; and edoxaban 30 mg once daily had significantly lower risk.[2,3,5] Factors associated with gastrointestinal bleeding with NOAC use are anemia, previous gastrointestinal bleeding, long term aspirin use or baseline nonaspirin antiplatelet use, age, diastolic hypertension, smoking, sleep apnea, chronic obstructive pulmonary disease, previous proton pump inhibitor use, renal dysfunction, and male sex.[46] Although gastrointestinal bleeding accounts for nearly 90% of major extracranial hemorrhages in NVAF patients on therapeutic anticoagulation,[47] clinical data specifically pertaining to NOAC reversal are lacking. Of the 3.3% of patients in the Dresden registry who experienced major bleeding while on rivaroxaban, the majority of patients were managed conservatively without requiring surgery.[48] As in the case of trauma, general resuscitation principles of airway, intravenous fluid, blood transfusion, and maintaining adequate urine output should be applied. A Blakemore tube for bleeding from esophageal varices may be considered. Immediate NOAC reversal should be considered in the unstable patient.

Reinitiating NOAC therapy after gastrointestinal bleeding should take into account the patient's underlying risk of bleeding and thrombosis risk. In a retrospective study of >4600 patients with NVAF who suffered gastrointestinal bleeding on anticoagulation (primarily warfarin), resumption of a single anticoagulant was associated with the lowest risk of mortality and thromboembolism compared with nonresumption of antithrombotic treatment. The risk of recurrent gastrointestinal bleeding was also low in the anticoagulated patients. Patients on NOACs comprised a very small subset of the entire cohort; therefore, it remains uncertain whether NOAC resumption after gastrointestinal bleeding would be similarly linked to these favorable outcomes.[49]

MANAGEMENT OF PATIENTS ON NOACS WHO ARE AT RISK FOR BLEEDING

Management of Patients Who Overdose on NOACs

Data regarding the prevalence of overdoses or unprescribed exposures to NOACs are largely based on observational data from poison control centers and case reports.[13,14,18,19,50–61] Stevenson et al reported that between January 2011 and July 2013, there were 49 calls to a single poison control center regarding dabigatran and rivaroxaban.[18] Of these, only 4 cases were a result of self-harm, and only mild bleeding was reported in 1 case. The majority of bleeding events were noted in patients on long-term treatment and not acute ingestions, and there was no association with coagulation abnormalities and risk of bleeding. Conway et al reported dabigatran exposures from a national poison control center and noted that adverse outcomes occurred in only 5% of all calls, and only 1.3% were considered intentional.[50] An observational study from poison control centers in 9 states showed that among 223 NOAC exposure calls related to rivaroxaban and apixaban ingestions, 42% had abnormal coagulation studies and no patient had bleeding.[51] Unfortunately, there is limited information to guide management of patients with NOAC overdose with and without bleeding. Collection of information on the type of NOAC, the ingested dose, time of ingestion, concomitant renal/liver disease, and relevant medication coingestion is critically important in the acute period. Therapeutic management strategies in the acute care setting have largely been developed on the basis of clinical experience and an understanding of the pharmacology rather than trial data.

Management of Patients With Acute Kidney Injury on NOACs

The risk of acute kidney injury is high in the patient population who are frequently prescribed NOACs. Andreu-Cayuelas et al performed an observational study of 162 patients with NVAF after hospitalization for acute heart failure. Creatinine was measured during follow-up to determine the need for dose adjustment of the hypothetical NOACs.[62] The investigators reported 44% of patients would have needed dabigatran dosage adjustment, 35% would have needed rivaroxaban adjustment, and 29% would have needed apixaban dosage adjustment. The patients with a baseline CrCl of <60 mL/min or age >75 years were at greatest risk of needing a dose adjustment during follow-up.[62]

VKA-associated nephropathy has recently been described as acute kidney injury with supratherapeutic international normalized ratio (INR) values with and without hematuria.[63–65] Alternatively, NOACs do not appear to be associated with kidney injury. In a meta-analysis conducted by Caldeira et al, NOACs did not increase the risk of renal failure (relative risk [RR], 0.96; 95% CI, 0.87–1.07; I^2=17.8%; 6 randomized controlled trials) when compared with a VKA.[63] A recent analysis of ROCKET AF revealed a small but statistically significant decline in mean CrCl± standard deviation among patients receiving warfarin (−4.3±14.6 mL/min) compared with patients receiving rivaroxaban (−3.5±15.1 mL/min; P<0.001).[66] A post hoc analysis of the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial similarly revealed greater declines in CrCl with warfarin compared with dabigatran.[67]

Administering a NOAC in a patient with acute kidney injury increases the risk of bleeding. All NOACs except apixaban are contraindicated in patients on hemodialysis on the basis of their respective US prescribing monograph. Although a dosing recommendation for apixaban is provided for such patients in the product monograph,

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this recommendation is based on pharmacokinetic data in fewer than 20 patients. There are no efficacy or safety data in this patient population. Until these data become available, close measurement or switching to an alternative anticoagulant is suggested for patients who develop acute kidney injury as a result of acute illness or injury.

Management of Patients With Ischemic Stroke on NOACs

Whereas NOACs represent a major advance in stroke prevention, it is still anticipated that acute ischemic stroke (AIS) will occur in 1% to 2% of individuals with NVAF treated with these agents each year.[2–5] Their use presents a number of challenges for clinicians managing patients with AIS, including appropriate measurement of anticoagulant activity in neurovascular emergencies, the role of thrombolysis and endovascular therapy in AIS, and timing of reinstitution of oral anticoagulation after AIS. Thrombolytic therapy with intravenous recombinant tissue-type plasminogen activator within 4.5 hours of symptom onset is an established treatment in AIS[68,69] but is associated with a >5-fold increase in the rate of ICH.[70] Because of the danger of further increasing ICH, therapeutic anticoagulation is considered a contraindication to thrombolytic therapy in AIS. AHA guidelines and observational data support intravenous thrombolysis in warfarin-treated patients provided the INR is no greater than 1.7.[71,72] The data on safety of thrombolysis in the presence of low levels of anticoagulation with warfarin raises hope that the same may apply to NOACs.

Determining appropriate treatment for AIS patients receiving NOACs must balance the anticoagulant effect of these agents and the ICH risk associated with reperfusion strategies. As has been mentioned previously, routinely performed blood coagulation studies do not reliably exclude a significant plasma concentration of the NOACs. Another difficulty in a time-sensitive setting is that the more sensitive blood tests are either not routinely available or have an unacceptably long delay to results. In experimental studies, pretreatment with dabigatran or rivaroxaban did not increase the rate of thrombolysis-associated ICH.[72,73] Data on the safety and efficacy of intravenous thrombolysis in AIS patients receiving NOACs are limited to approximately 2 dozen case reports and a retrospective multicenter cohort study. Among the case reports, ICH and poor outcome were rarely reported when recombinant tissue-type plasminogen activator was administered minutes to 24 hours after the last anticoagulant dose.[74,75] The cohort study[76] comprised 78 NOAC-treated patients undergoing intravenous thrombolysis or intra-arterial therapy a median of 13 hours after the last NOAC dose compared with 441 warfarin-treated patients and 8938 on no anticoagulants. After propensity score matching, there was no significant difference in rate of any ICH, symptomatic ICH, or death among the groups. In the absence of immediately available blood tests sensitive to the presence of NOACs, determining which patients taking these agents might be appropriate candidates for thrombolysis requires consideration of time from last dose, half-life of the agent used, and presence of impaired renal function that may reduce drug clearance. A new recommendation in the AHA "Guidelines for the Early Management of Patients With Acute Ischemic Stroke" is that recombinant tissue-type plasminogen activator should not be administered to patients who take NOACs unless sensitive laboratory tests are normal or the patient has not received a dose of these agents for >48 hours.[71]

Data guiding the use of endovascular therapy in AIS patients who take NOACs are even more limited. Among the pivotal trials that established the safety and efficacy of mechanical thrombectomy in patients with AIS and large vessel occlusion, patients receiving NOACs were either excluded[77] or not specifically reported.[78–81] A handful of case reports suggest safety of endovascular therapy in patients on dabigatran and rivaroxaban even in the setting of abnormal coagulation studies.[82–87] In the previously described cohort study, none of the 33 patients who underwent endovascular therapy with or without intravenous thrombolysis experienced a symptomatic ICH. Reflecting the paucity of data in this area, the AHA's guidelines provide no recommendations regarding mechanical thrombectomy in patients whose use of anticoagulant medications excludes them from intravenous thrombolysis.[88]

The optimal timing of restarting anticoagulation after AIS presents another challenge to healthcare professionals managing this population. Meta-analysis of 7 trials of parenteral anticoagulation started within 48 hours of cardioembolic ischemic stroke[89] and systematic review of 24 trials involving 23 748 participants with AIS[90] testing various parenteral and oral anticoagulants each concluded that while early anticoagulation is associated with a reduced risk of recurrent ischemic stroke, this benefit is entirely offset by an increased risk of symptomatic ICH with no reduction in risk of death or dependency.

The decision of when to restart oral anticoagulation must balance the competing risks of recurrent thromboembolic events and of hemorrhagic transformation. Consideration is given to the type of event (transient ischemic attack versus cerebral infarct), time from stroke onset, and presence of factors associated with increased hemorrhage risk (large infarct size, uncontrolled blood pressure, hyperglycemia, thrombocytopenia, previous hemorrhagic stroke, and thrombolytic treatment).[70,91] Hemorrhagic transformation of ischemic brain tissue is a relatively common occurrence that is often asymptomatic or minimally symptomatic and uncommonly progresses in extent in the absence of predisposing factors.[92,93] Assuming the hemorrhagic transformation is asymptomatic and remains stable, case series support

the safety of starting or continuing warfarin in carefully selected patients with a compelling indication.[94] Whether optimal timing of resumption of oral anticoagulation with NOACs should follow similar recommendations is unknown. Differences in the pharmacological properties of warfarin and the NOAC must be considered, notably the more rapid time to anticoagulant effect with the NOACs (a few hours compared with 4 to 5 days for warfarin). In experimental models of ischemic stroke, neither dabigatran pretreatment nor continued administration of dabigatran after stroke onset significantly increased the risk or volume of hemorrhagic transformation after middle cerebral artery occlusion.[95,96] Clinical data are anecdotal only. The phase III trials establishing the role of NOACs for stroke prevention in NVAF excluded patients within 7 to 30 days of stroke.[2–5,97] In general, guidelines support withholding oral anticoagulation until 1 to 2 weeks after stroke among individuals with NVAF, with shorter times for those with transient ischemic attack or small, nondisabling strokes and longer times for moderate to severe strokes.[98–100] In NOAC-treated patients who have an AIS, compliance with NOAC therapy should be established and alternative causes for the stroke investigated. There are no data to indicate that increasing the intensity of anticoagulation, adding an antiplatelet agent, or switching to another oral anticoagulant provides additional protection against future ischemic events. Because of the short half-lives of NOACs and rapid decline of protective anticoagulation that occurs with missed doses, patients with poor compliance might be more appropriately managed with the longer-acting warfarin.

TRANSITIONING BETWEEN NOACS AND OTHER ANTICOAGULANTS IN THE ACUTE CARE SETTING

Indications that require considerations for the transitioning of anticoagulants in the acute care setting include the occurrence of a new clinical event (eg, myocardial infarction) in patients on established oral anticoagulant regimens, the development of a new or worsening comorbid medical condition (eg, renal failure) that necessitates an anticoagulant transition and the need for an invasive procedure. In the United States, the current labeled prescribing information for each NOAC provides guidance for the transition to and from NOAC agents to other anticoagulants; however, these suggestions are not specific for patients in the acute care setting (Table 3).[33,43,101,102]

Temporary interruptions in oral anticoagulation are commonly encountered in the acute care setting. On the basis of trial observations from NOAC agents in patients with AF, approximately one third of AF patients will experience the need for a temporary interruption over the course of 2 years.[103–105] The association of temporary interruptions in oral anticoagulant therapy with the risk for clinical events has been reported in 3 of the clinical trials comparing NOAC agents to VKAs in patients with AF.[103–105] In addition, a meta-analysis using data from trials comparing the risk of thromboembolic events associated with temporary discontinuation found no statistically significant differences in the NOAC versus VKA randomized groups (RR, 1.01; 95% CI, 0.68–1.49).[106] Whereas the majority of the temporary interruptions in the trials were around procedures, the use of periprocedural bridging regimens varied on the basis of patient characteristics and trial protocols. Only 6% and 11.7% of patients with temporary oral anticoagulation interruption received bridging in ROCKET AF and the ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), respectively.[104,105]

Much of the clinical outcome data regarding the switching or transitioning between NOAC agents and other anticoagulants comes from the clinical trials in patients with NVAF. Observations from trials reported the risk of embolic and bleeding events in the NOAC and VKA treatment groups associated with the transitions at the beginning and end of the trials have been published. A post hoc analysis of ROCKET AF reported an increased risk of stroke in the rivaroxaban treatment group during the end-of-study transition to the open-label therapy period.[107] Patients who received rivaroxaban compared with those who received warfarin were observed to have an increased incidence of stroke during the period of transition (3 to 30 days after the end of the study) to open-label therapy (n=22 versus n=6; hazard ratio [HR], 3.72; 95% CI, 1.51–9.16) as well as a greater proportion of major bleeding events (n=25 versus n=7; HR, 3.62; 95% CI, 1.56–8.36).[107,108] In addition, during the end-of-study transition period, the median time to first therapeutic INR was 3 days in the warfarin treatment group compared with 13 days in the rivaroxaban treatment group.[108] Similar observations of an increased risk of clinical events in those assigned to NOAC therapy have been reported from the ARISTOTLE trial end-of-study open-label transition period.[109] At the end of ARISTOTLE, a 2-day bridging period with apixaban or apixaban placebo was recommended during the initiation of open-label VKAs. During the first 30 days after stopping blinded study drug, 21 stroke or systemic embolism events were noted in the apixaban group versus 5 in the warfarin group (adjusted HR, 4.10; 95% CI, 1.54–10.86). An excess in major bleeding events was also observed during this period in the apixaban versus warfarin groups (n=26 versus n=10; adjusted HR, 2.56; 95% CI, 1.23–5.30). On the basis of these observations, an end-of-study transition plan was designed for patients enrolled in the ENGAGE AF (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation) trial.[110] In brief, for patients who were planned to transition to open-label NOAC therapy, mea-

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Table 3. Overview of US-Labeled Guidance for NOAC Anticoagulant Transitions

NOAC	VKA	Intravenous Anticoagulant	LMWH/Other NOAC
Apixaban	Apixaban→warfarin: Discontinue apixaban and begin a parenteral anticoagulant and warfarin at the time the next scheduled apixaban dose would have been taken	Apixaban→parenteral anticoagulant: Discontinue apixaban and begin the new anticoagulant at the usual time of the next dose of apixaban	Apixaban→LMWH/other NOAC: Discontinue apixaban and begin the LMWH/other NOAC at the usual time of the next dose of apixaban
	Warfarin→apixaban: Discontinue warfarin and start apixaban when INR <2.0		LMWH/other NOAC→apixaban: Discontinue current NOAC/LMWH and begin apixaban at the usual time of the next dose of the other NOAC/LMWH
Dabigatran	Dabigatran→warfarin: For CrCl ≥50 mL/min, start warfarin 3 d before discontinuing dabigatran For CrCl 30–50 mL/min, start warfarin 2 d before discontinuing dabigatran For CrCl 15–30 mL/min, start warfarin 1 d before discontinuing dabigatran	Dabigatran→parenteral anticoagulant: Wait 12 h (CrCl ≥30 mL/min) or 24 h (CrCl <30 mL/min) after last dabigatran dose before initiating a parenteral anticoagulant	Dabigatran→LMWH: Wait 12 h (CrCl >30 mL/min) or 24 h (CrCl <30 mL/min) after last dabigatran dose before initiating a parenteral anticoagulant
	Warfarin→dabigatran: Discontinue warfarin and start dabigatran when INR <2.0	UFH→dabigatran: Start dabigatran at the time of continuous infusion discontinuation	LMWH→dabigatran: Start dabigatran 0–2 h before the time that the next LMWH dose would have been given
Edoxaban	Edoxaban→warfarin: Oral option: Reduce daily edoxaban dose by 50% and begin taking warfarin concomitantly. Measure INR at least weekly just before daily edoxaban dose. Once a stable INR ≥2.0 is achieved, discontinue edoxaban and continue warfarin Parenteral option: Discontinue edoxaban and administer a parenteral anticoagulant and warfarin at the time of the next scheduled edoxaban dose.	Edoxaban→parenteral anticoagulant: Discontinue edoxaban and start the parenteral anticoagulant at the time of the next scheduled dose of edoxaban	Edoxaban→LMWH/other NOAC: Discontinue edoxaban and start the LMWH/other NOAC at the time of the next scheduled dose of edoxaban
	Warfarin→edoxaban: Discontinue warfarin and start edoxaban when the INR is <2.5	UFH→edoxaban: Discontinue UFH infusion and start edoxaban 4 h later	LMWH/other NOAC→edoxaban: Discontinue current NOAC/LMWH and start edoxaban at the time of the next scheduled other NOAC/LMWH dose
Rivaroxaban	Rivaroxaban→warfarin: Discontinue rivaroxaban and begin a parenteral anticoagulant and warfarin at the time the next scheduled rivaroxaban dose would have been taken	Rivaroxaban→UFH: Discontinue rivaroxaban and initiate the parenteral anticoagulant at the time the next rivaroxaban dose would have been taken	Rivaroxaban→LMWH/other NOAC: Discontinue rivaroxaban and start the LMWH/other NOAC at the time of the next scheduled dose of rivaroxaban
	Warfarin→rivaroxaban: Discontinue warfarin and start rivaroxaban as soon as INR <3.0	UFH→rivaroxaban: Stop UFH infusion and administer rivaroxaban at the same time	LMWH/other NOAC→rivaroxaban: Start rivaroxaban 0–2 h before the next scheduled evening LMWH/other NOAC dose and omit administration of the LMWH/other NOAC

CrCl indicates creatinine clearance; INR, international normalized ratio; LMWH, low-molecular-weight heparin; NOAC, non–vitamin K antagonist oral anticoagulant; UFH, unfractionated heparin; and VKA, vitamin K antagonist.

surement of INR was conducted and the open-label NOAC was initiated when the INR was <2.0. For patients transitioning to a VKA, a 14-day kit was provided that included a VKA algorithm and a modified dose of edoxaban, which was to be continued until day 14 or an open-label INR ≥2.0, whichever occurred first. Within 30 days of study drug discontinuation, strokes were observed to occur in 7 patients in each of the 3 study treatment groups with major bleeding events noted in 11 patients in the warfarin group, 10 patients in the edoxaban high-dose

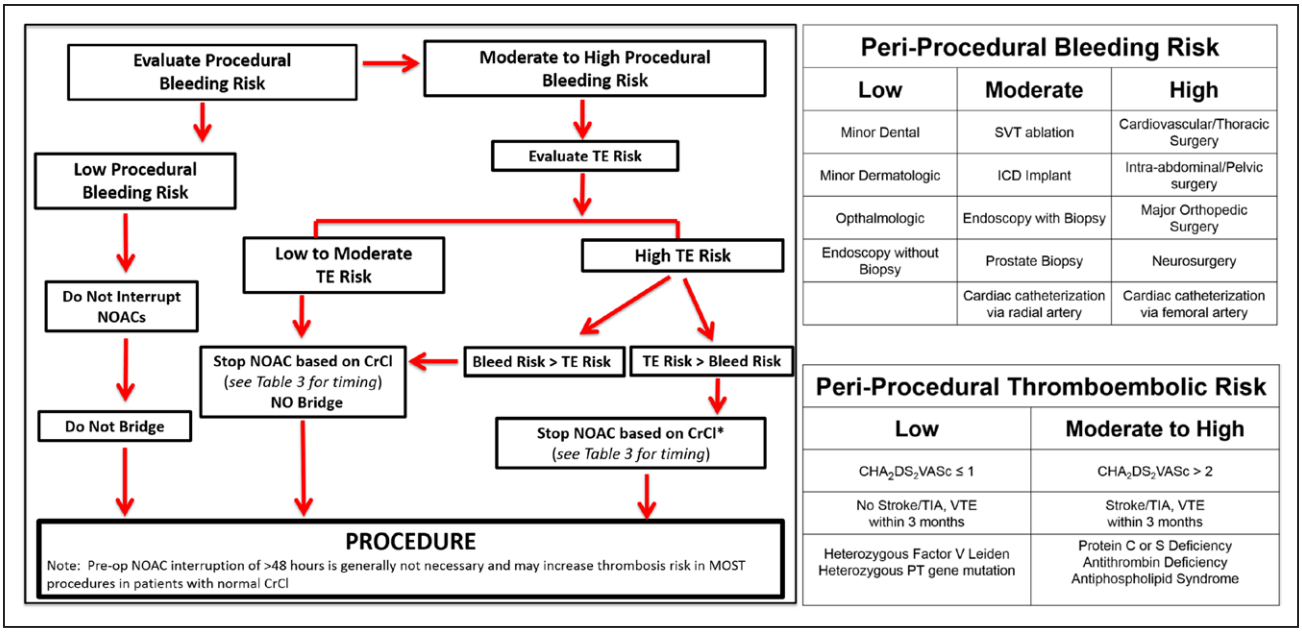

Figure 3. Periprocedural management of patients on NOACs (non–vitamin K antagonist oral anticoagulants).
CrCl indicates creatinine clearance; ICD, implantable cardioverter-defibrillator; PT, prothrombin time; SVT, supraventricular tachycardia; TE, thromboembolic event; TIA, transient ischemic attack; and VTE, venous thromboembolism.
*Bridging may be considered in patients with a history of systemic embolus in the last 6 weeks.[110a]

group, and 18 patients in the edoxaban low-dose group. No statistically significant differences were observed in primary efficacy or safety events among the 3 treatment groups in patients transitioning to open-label VKAs or in those transitioning to open-label NOACs.[110] It is notable that in patients transitioning to open-label VKAs, 85% had at least 1 INR ≥2 by day 14.

Registry data on the outcomes of ambulatory AF patients transitioning from a VKA to a NOAC (dabigatran or rivaroxaban) have also been published.[111,112] In a matched-cohort study of AF patients, there was no association of transitioning from a VKA to either dabigatran or rivaroxaban compared with remaining on VKA therapy for embolic or bleeding events at a median follow-up of 10 months.[112] Data from a large regional prospective registry showed clinical events were relatively infrequent in the 30-day period after VKA to NOAC transitions despite only 75% of patients having an INR measurement before NOAC initiation.

Although clinical decisions regarding the transition between anticoagulants in the acute care setting are likely to be affected by a number of factors, careful consideration should be given to strategies that minimize prolonged durations of both subtherapeutic and excessive anticoagulation during the transition periods. Given the relatively infrequent use of periprocedural bridging strategies during temporary interruptions in the clinical trials, clinical consideration should be given to managing patients experiencing temporary interruptions without bridging, as outlined in the individual NOAC trials.

PERIPROCEDURAL MANAGEMENT OF PATIENTS WHO TAKE NOACS

Each year, ≈10% of patients on any long-term oral anticoagulation require surgery or other invasive procedures.[113] Approximately 20% of patients on warfarin undergo surgery that has an extremely low risk of bleeding such as minor dental, dermatologic, or ophthalmologic procedures where anticoagulation may be safely continued without interruption.[114] It is recommended that warfarin be held for 5 days before surgery when significant bleeding is anticipated and then reinitiated postoperatively when hemostasis is secured.[115] Pre- and postoperative bridging using low-molecular-weight heparin is recommended for those patients with high thrombosis risk, such as those with certain mechanical valve prostheses or recent pulmonary embolism. In patients at low to intermediate risk of thrombosis, bridging low-molecular-weight heparin does not prevent thrombotic events and increases bleeding events[116] (Figure 3). Therefore, bridging anticoagulation is not necessary in this subgroup of patients.

The limited data available pertaining to patients on NOAC therapy who require surgery suggest that the perioperative bleeding risk is low for nonurgent surgery. The Dresden NOAC registry prospectively evaluated 2179 patients taking NOACs, of which 595 patients (27.3%) underwent 863 invasive procedures; most were not urgent.[48] Invasive procedures were categorized as major or minor, and a bleeding event was categorized as major, clinically relevant nonmajor, or minor per the International Society of Thrombosis and

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Haemostasis definition.[117] Of the entire cohort, only 46 patients (5.3%) experienced any bleeding complication up to 30±5 days after the procedure. Major bleeding occurred in 10 of 863 (1.2%) procedures. Clinically relevant nonmajor bleeding occurred in 29 patients (3.4%) and minor bleeding occurred in only 7 patients (0.8%). Periprocedural bleeding was studied in a subgroup analysis of the RELY trial which compared warfarin to dabigatran for stroke prevention in NVAF.[103] Procedures were classified as being associated with a low (coronary angiography, defibrillator implantation) or high risk of bleeding (cardiac, abdominal, and neurosurgery, or procedures requiring spinal anesthesia). There was no significant difference in the rates of periprocedural major bleeding between patients who received dabigatran 110 mg (3.8%), dabigatran 150 mg (5.1%), or warfarin (4.6%); dabigatran 110 mg versus warfarin: RR, 0.83; 95% CI, 0.59 to 1.17; *P*=0.28; dabigatran 150 mg versus warfarin: RR, 1.09; 95% CI, 0.80 to 1.49; *P*=0.58. Among patients who had urgent surgery, major bleeding was increased, occurring in 17.8% with dabigatran 110 mg, 17.7% with dabigatran 150 mg, and 21.6% with warfarin: dabigatran 110 mg: RR, 0.82; 95% CI, 0.48 to 1.41; *P*=0.47; dabigatran 150 mg: RR, 0.82; 95% CI, 0.50 to 1.35; *P*=0.44. Tailoring periprocedural NOAC management to the type of invasive procedure may mitigate against bleeding. Common clinical scenarios are subsequently discussed.

Cardiac Catheterization and Percutaneous Coronary Intervention

Patients with AF commonly have coexisting coronary artery disease with an estimated 20% requiring percutaneous coronary intervention (PCI).[118] The 2012 American College of Cardiology/Society for Cardovascular Angiography and Interventions consensus document recommends that elective coronary angiography for patients on long-term warfarin be deferred until the INR is 1.8 for femoral artery access or <2.2 for radial artery access.[119] Unfortunately, there are very limited data that address the management of patients on a NOAC who require cardiac catheterization or PCI. Pre-, peri-, and postprocedural considerations are subsequently discussed.

Preprocedural Considerations

Patients with stable ischemic heart disease with ischemic symptoms despite medical therapy or with intermediate- or high-risk features on stress testing are often referred for coronary angiography and possible PCI. Patients with stable ischemic heart disease on a NOAC and who are not at high thrombosis risk should have the NOAC held until the anticoagulation effect is dissipated before undergoing coronary angiography and PCI. From the prescribing information, dabigatran should be held for at least 24 hours if CrCl ≥50 mL/min; for at least 72 hours if CrCL <50 mL/min; rivaroxaban, apixaban and edoxaban should be held for at least 24 hours.[33,43,101,102]

In the absence of high risk features, patients should not be bridged with a heparin before or after the procedure.[116] The decision to resume antithrombotic therapy after the procedure should be guided by the thromboembolic risk as assessed by the CHA_2DS_2-VASc score.[120] Clinicians need to consider which antithrombotic and antiplatelet agents to resume and the duration of antiplatelet therapy, balancing ischemic and thrombotic events while minimizing the hemorrhagic complications.

Patients presenting with an acute coronary syndrome (ACS) often undergo coronary angiography and revascularization to reduce their risk of recurrent events, especially if they have an elevated Thrombolysis in Myocardial Infarction (TIMI) risk score.[121] Whereas patients with unstable angina or a non–ST-segment elevation myocardial infarction do not require immediate angiography, patients presenting with a ST-segment elevation myocardial infarction require emergency coronary angiography and revascularization of the infarct related artery.[122] For the unstable angina/non–ST-segment elevation myocardial infarction patient, appropriate dual antiplatelet therapy (DAPT) and heparin therapy should be started upstream, the NOAC should be discontinued and the patient should be scheduled for an urgent catheterization. In the absence of electrical or hemodynamic instability, it is reasonable to wait for the effects of the NOAC to dissipate and then perform the procedure through a radial artery approach.

Periprocedural Considerations

Patients on NOACs undergoing coronary angiography or PCI will have an increased risk of hemorrhagic complications, and therefore, careful attention should be made to choice of vascular access site and use of adjunctive anticoagulants. Patients should undergo radial artery access, unless there is a contraindication, because the risk of bleeding and vascular complications is reduced as compared with a femoral approach.[123] If a femoral approach is required, one should consider using ultrasonography and fluoroscopy to guide vascular access. A micropuncture needle technique may decrease the probability of a retroperitoneal bleed. Although no data exist, it may be reasonable to use a vascular closure device to assist with postprocedure hemostasis if the patient has amenable vascular anatomy. Venous access should be avoided unless absolutely required. All patients undergoing PCI require antiplatelet therapy coupled with either heparin or bivalirudin to reduce the periprocedural thrombotic complication rates, irrespective of background use of

VKAs or NOACs.[124] The use of intravenous glycoprotein agents should be discouraged and reserved for bailout scenarios. For patients who receive intravenous heparin, one should use low-dose heparin regimens with an activated clotting time goal of ≈250 seconds to reduce hemorrhagic complications.[125]

Postprocedural Considerations

The clinician should consider the patient's risk of recurrent myocardial infarction, stent thrombosis, thromboembolic risk, and hemorrhagic complications when selecting anticoagulants. It is helpful to use the CHA_2DS_2-VASc risk score to estimate the thromboembolic risk and the HAS-BLED risk score to estimate the hemorrhagic risk and include the patient in a shared decision regarding the selection of DAPT versus triple therapy as well as the duration of therapy. Several themes have emerged. The standard of care to reduce coronary ischemic events post-PCI and post-ACS is DAPT. The duration of DAPT is directly impacted by the stent type (bare metal stent versus drug-eluting stent) and whether the patient underwent PCI for stable ischemic heart disease or ACS.[126] However, oral antithrombotic agents (not antiplatelet agents) are required to prevent NVAF related stroke or VTE. Therefore, the clinician is faced with the consideration of DAPT, DAPT plus warfarin (triple therapy), DAPT plus a NOAC (triple therapy) or warfarin plus single antiplatelet therapy.

In a phase II study, triple therapy with dabigatran in patients with ACS was associated with an increased risk of bleeding complications and planned phase III trials were not pursued.[127] In a randomized clinical trial of patients with ACS, apixaban increased bleeding without reducing ischemic event in patients on either DAPT or aspirin alone. Intracranial bleed rates were increased in patients treated with apixaban. Because of concerns regarding safety without a signal of efficacy, the trial was terminated.[128] Rivaroxaban was studied in the ATLAS ACS-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin With or Without Thienopyridine Therapy in Subjects With Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction) trial, which compared rivaroxaban or placebo in addition to standard ACS therapies. Compared with placebo, rivaroxaban (2.5 mg twice daily and 5.0 mg twice daily) decreased the rates of the composite primary end point including cardiovascular death, myocardial infarction or stroke (10.7% versus 8.9%) while increasing the rates of bleeding (non–coronary artery bypass graft surgery) and ICH.[129] Only rivaroxaban coupled with DAPT has been demonstrated to reduce ischemic events at a cost of increased bleeding. However, the studied doses of rivaroxaban are not the doses proven to reduce the risk of thromboembolic events secondary to AF.

European and Canadian guidelines suggest NOACs are preferred over warfarin when it comes to triple therapy. However, these recommendations are based on observational data and post hoc analysis of warfarin vs. NOAC studies with limited number of patients. For example, in ROCKET AF, only 1% of patients underwent PCI during the trial.[130] Until further prospective, randomized trial data become available on the subject, the AHA writing group suggests that clinicians use good judgment, weighing the risk/benefits of NOACs in the context of triple therapy for their patients.

Proton pump inhibitors decrease the rates of upper gastrointestinal bleeding in patients with DAPT and in patients with DAPT and antithrombotic therapy.[131] Patients should be advised to avoid nonsteroidal anti-inflammatory medications as the risks of myocardial infarction and hemorrhagic complications are increased. Ongoing randomized trials (Pioneer AF-PCI [Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention],[132] RE-DUAL PCI [Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting], RT-AF [Rivaroxaban in Patients With Atrial Fibrillation and Coronary Artery Disease Undergoing Percutaneous Coronary Intervention],[133] SAFE-A [Safety and Effectiveness Trial of Apixaban Use in Association With Dual Antiplatelet Therapy in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention][134] and AUGUSTUS [A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart]) will assess the efficacy of a NOAC coupled with antiplatelet therapy in patients undergoing PCI. Until these trials are completed and published, the writing group makes the following suggestions:

1. For patients with a CHA_2DS_2-VASc score of 0 or 1 treated with PCI, it is reasonable to omit anticoagulant therapy and treat with DAPT.
2. For patients who require DAPT or triple therapy, use low-dose aspirin, 81 mg daily.
3. For stable ischemic heart disease patients who require anticoagulant therapy and treatment with PCI, discontinuation of $P2Y_{12}$ inhibitor therapy after 3 months may be reasonable.[126]
4. For ACS patients requiring anticoagulant therapy and treatment with PCI (bare metal stent or drug-eluting stent), continuation of aspirin 81 mg daily for 1 year and discontinuation of $P2Y_{12}$ therapy after 6 months may be reasonable.[126]
5. For patients with a moderate to high risk of bleeding, as assessed by the HAS-BLED score, a shortened duration of triple therapy or warfarin plus clopidogrel may be considered based on the exploratory WOEST (What Is the Optimal Antiplatelet

and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting) trial.[135]

6. Prasugrel and ticagrelor should not be used in conjunction with NOACs, as a result of excessive bleeding risk.
7. At present, there are limited data to recommend the routine use of NOACs, coupled with clopidogrel alone or DAPT after PCI. Of note, in clinical practice, it can be challenging to reach and maintain therapeutic warfarin levels in certain patients. In these patients, it may be reasonable to combine a NOAC and clopidogrel after PCI.

Cardioversion of AF

Post hoc analyses from pivotal NOAC clinical trials have not shown significant differences in outcomes after cardioversion in those treated with NOACs compared with warfarin.[136–138] Meta-analysis of events across randomized trials appears to confirm these results, finding no significant difference in stroke/systemic embolism (odds ratio, 0.73; 95% CI, 0.31–1.72) or major/nonmajor clinical relevant International Society on Thrombosis and Haemostasis bleeding events (odds ratio, 1.41; 95% CI, 0.87–2.28) after cardioversion.[139,140] Moreover, there is 1 randomized clinical trial of cardioversion in patients treated with a factor Xa inhibitor versus warfarin. More than 1500 patients undergoing early (target period of 1 to 5 days after randomization with transesophageal echocardiography [TEE]) or delayed (3 to 8 weeks) cardioversion were randomized in a 2:1 fashion to rivaroxaban or warfarin. The primary efficacy end point (composite of stroke, transient ischemic attack, peripheral embolism, myocardial infarction, and cardiovascular death) occurred in 0.51% of the rivaroxaban patients versus 1.02% of the VKA-treated patients (RR, 0.50; 95% CI, 0.15–1.73) with no significant difference in bleeding observed.[141]

Observational data from clinical practice demonstrate similar findings. Data from a large nationwide cohort study demonstrated no difference between outcomes in those treated with dabigatran versus warfarin. In 1230 patients undergoing cardioversion, the cumulative incidence of stroke, bleeding or death at 30 weeks was 2.0% in those treated with warfarin and 1.0% in those treated with dabigatran (adjusted HR, 1.33; 95% CI, 0.33–5.42).[142] High-volume single-center data (>4600 cardioversions) have also failed to identify any difference in postcardioversion thromboembolic or bleeding events across warfarin and NOAC agents.[143]

The ENSURE-AF trial (Edoxaban Versus Enoxaparin-Warfarin in Patients Undergoing Cardioversion of Atrial Fibrillation) randomized 2199 patients to either edoxaban or enoxaparin/warfarin during TEE or non-TEE guided electrical cardioversion.[144] For TEE-guided cardioversion, randomization occurred <3 days from cardioversion and study treatment was continued for at least 28 days. For non–TEE-guided cardioversion, study treatment was initiated at least 21 days before cardioversion and extended for at least 28 days. The primary efficacy end point (composite of stroke, systemic embolic event, myocardial infarction, and cardiovascular mortality) and the primary safety end point (major and clinically relevant nonmajor bleeding) occurred at a statistically similar frequency. Edoxaban may be an effective and safe alternative to enoxaparin/warfarin for patients with NVAF requiring cardioversion.

Several practical considerations must be weighed when cardioverting patients on NOAC therapy with AF duration >24 hours. Similar to recommendations with warfarin, patients should be anticoagulated for a minimum of 3 weeks before elective cardioversion. If not, then a TEE should be performed to exclude the presence of left atrial appendage or left atrial thrombus. Similarly, if a given patient's adherence to therapy is suboptimal (≥2 missed doses) or in question, then a TEE should be considered. If a patient has been on a properly dosed NOAC with 3 weeks of therapy and is found to have left atrial appendage or left atrial thrombus, then consideration should be given to switching to an alternate anticoagulant with special attention to consistent anticoagulant use during the transition.

Catheter Ablation of AF

Catheter ablation is an increasingly used treatment option for rhythm control in NVAF. Because of the risks of periprocedural thromboembolism, anticoagulation is required during the procedure. However, the presence of anticoagulation can make the management of bleeding complications more difficult. Before the advent of NOAC therapy, observational[145,146] and randomized[147] studies suggested that uninterrupted VKA therapy was associated with superior outcomes compared with VKA interruption with intraprocedural heparin. In particular, the COMPARE (Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation [AF] Patients Undergoing Catheter Ablation) clinical trial randomized 1584 patients to interrupted warfarin with bridging anticoagulation (n=790) versus continuous warfarin (n=794). Bleeding events were less common in the continuous warfarin arm with no significant difference in stroke or transient ischemic attack (0.4% versus 0.8% major bleeding, 0.5% versus 0.9% pericardial effusion, and 4% versus 22% minor bleeding).[147]

How interrupted/continuous NOAC therapy compares to continuous warfarin has been the subject of intense study over the past 5 years. Multiple systematic assessments and meta-analyses have demonstrated similar outcomes in patients treated with NOACs (interrupted or continuous) versus continuous warfarin.[148–152] One randomized study compared uninterrupted rivaroxaban and VKA in 248 patients. The occurrence of any thromboembolic events (0 versus 2) and bleeding events (21 versus 18) was similar in the uninterrupted rivaroxaban and VKA arms. Although the study was relatively

small with limited power, the results were largely in line with previous observational data that have suggested similar outcomes with NOAC and VKA therapy. Another randomized study compared uninterrupted apixaban versus continuous warfarin in 200 subjects with drug-refractory AF undergoing ablation and found no difference in thromboembolic or bleeding outcomes.[153] There are several ongoing larger randomized clinical trials of interrupted versus uninterrupted NOAC therapy and continuous warfarin versus continuous NOAC therapy.

The recommendation to use TEE to exclude the presence of left atrial appendage/left atrial thrombus should be similar regardless of whether VKA or NOAC therapy is used.[154] If the patient has not had 3 to 4 weeks of preprocedural anticoagulation or if the patient is considered at increased risk for stroke, the use of TEE is mandatory. However, many laboratories conduct a TEE in all patients before ablation since thrombus can be observed even in low-risk patients with paroxysmal AF.[155]

Regardless of whether continuous or interrupted NOAC therapy is used, on the basis of current consensus recommendations, patients should be heparinized with 100-U/kg bolus followed by an infusion of 10 U/kg/hour before or immediately after puncture. The activated clotting time should be checked every 10 to 15 minutes until target and then every 30 minutes thereafter. The activated clotting time target should be at least 300 to 350 seconds or 350 to 400 seconds in the case of spontaneous echocardiographic contrast ("smoke") or severe left atrial enlargement.[154] Heparinization before transeptal access may be associated with a lower risk of asymptomatic microembolic events as detected by brain magnetic resonance imaging.[156] It is important to note that the use of NOAC therapy before and during the procedure results in the need for an increased dose of heparin to achieve target activated clotting times during the ablation procedure.[157] After the procedure, NOAC therapy is generally reintroduced within 4 to 8 hours after sheath removal if access site hemostasis has been achieved. Consistent with consensus recommendations, NOAC therapy should be continued for a minimum of 2 to 3 months after ablation. Thereafter, oral anticoagulation should be based on the patient's underlying risk for stroke (CHA_2DS_2-VASc score) rather than the current rhythm.

Electronic Device Implantation

Management of oral anticoagulation surrounding cardiac implantable electronic device insertion presents several challenges. Oral anticoagulation increases the risk of bleeding and hematoma formation after device implantation. Furthermore, hematoma formation increases the risk of postoperative infection. Based upon the results from randomized clinical trials, uninterrupted warfarin has been shown to lead to less bleeding and superior outcomes compared with interrupted warfarin and parenteral bridging therapy.[158,159] These findings are also consistent with the BRIDGE (Perioperative Bridging Anticoagulation in Patients With Atrial Fibrillation) trial, which found no significant benefit to bridging for general interruption of oral anticoagulation for invasive procedures in patients with NVAF.[116] However, the optimal management of NOAC therapy surrounding cardiac implantable electronic device implantation remains unknown.

In general, discontinuation of NOAC therapy before cardiac implantable electronic device implantation in a manner consistent with the elimination half-life is the most common practice pattern. For apixaban, edoxaban, and rivaroxaban, this would include discontinuation 24 hours in advance of the procedure. In the case of dabigatran, discontinuation is recommended 24 hours before in patients with a CrCl ≥80 mL/min, 36 hours before in those with CrCl 50 to 79 mL/min, and 48 hours before in those with a CrCl <50 mL/min.[160] Survey data from implanting physicians suggest wide variation in practice patterns reflecting the uncertainly over optimal management.[161] However, the majority of physicians discontinue NOAC therapy at the time of implantation (82%).[161] Although uninterrupted warfarin has the best evidence base (>1 randomized trial), an increasing number of cardiac implantable electronic device patients are taking NOAC therapy. Whether NOAC therapy can be continued through cardiac implantable electronic device implantation remains debated and is the subject of a large clinical trial (BRUISE CONTROL-2 [Strategy of Continued vs Interrupted Novel Oral Anticoagulant at Time of Device Surgery in Patients With Moderate to High Risk of Arterial Thromboembolic Events] study) in which perioperative management will be randomized to a strategy of continued versus interrupted NOAC therapy. The few available observational data are limited by their small cohort size but have not identified significant risks of bleeding with uninterrupted NOAC therapy.[162,163] When a decision is made to interrupt NOAC therapy for cardiac implantable electronic device implantation, the implanting physician must decide when the NOAC therapy should be restarted. This decision is often influenced by patient characteristics, including risk factors for bleeding and the postimplantation physical examination (eg, hematoma). Similar to discontinuation, practice patterns regarding resumption of NOAC therapy after implantation are highly variable.[161] Typically, NOAC therapy was restarted 24 to 48 hours after surgical procedures in the pivotal NOAC trials. Patients with multiple risk factors for bleeding, concomitant antiplatelet therapy, or evidence of hematoma on their postoperative examination may benefit from a greater delay to NOAC resumption (3 to 5 days). However, given the lack of evidence to guide these decisions, management should be approached on a patient-by-patient basis, weighing the risks and benefits of earlier versus later resumption of NOAC therapy.

Cardiovascular Surgery

There is limited information regarding the use of NOACs in coronary artery bypass grafting or valve replacement surgery. At present, information related to perioperative NOAC use in cardiac surgery is anecdotal or based on limited subset analyses.[48,164,165] No significant bleeding event differences were observed between rivaroxaban and warfarin treated patients who underwent cardiac surgery in ROCKET AF.[110a] The ATLAS ACS-2-TIMI-51 trial tested rivaroxaban to lower cardiovascular events in patients with ACS and reported 10 patients undergoing coronary artery bypass grafting after ST-segment elevation myocardial infarction.[129,166] Per the trial protocol, the drug was stopped 12 hours before the procedure and resumed 12 hours after the postprocedural drains were removed or after the last dose of parenteral anticoagulant therapy had been administered. The results specific to this group were not reported; therefore, no conclusions regarding coronary artery bypass grafting–related care can be made.

Established indications for NOACs in the pericardiac surgery setting include stroke prevention in preoperative AF, prolonged or frequent postoperative AF, and VTE treatment. NOAC use is contraindicated in patients with mechanical valves; as the RE-ALIGN (The Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients After Heart Valve Replacement) trial with dabigatran demonstrated, there is an increased rate of thromboembolic and bleeding complications compared with warfarin.[167] There are case reports of dabigatran use after left ventricular assist device placement[168] and of rivaroxaban use for heparin induced thrombocytopenia after coronary artery bypass grafting.[169] However, these off-label uses are not supported by available clinical trial evidence.

For cardiac surgery, NOACs should be stopped in the perioperative setting and restarted after clinical hemostasis has been established. As cardiac surgery is considered a high-bleeding-risk procedure, surgery should be postponed if at all possible until after the appropriate interruption period. Bleeding after cardiac surgery should be monitored via standard postprocedure drains. Life-threatening bleeding should be treated with supportive therapy, including transfusion of blood products and administration of antifibrinolytics as indicated for hemorrhage resuscitation, and return to the operating room. If contributing to an ongoing coagulopathy, administration of NOAC antidotes as previously described (Laboratory Measurement of NOAC Effect) could be considered. Mild bleeding may be monitored, but NOACs should not be reinitiated until there is bleeding control.

Similarly, the published experience of NOAC management in patients undergoing vascular surgery is limited to case reports and very small trial subsets.[48,164,165] In a subgroup analysis of ROCKET AF, patients with peripheral artery disease on rivaroxaban had a higher risk of major bleeding and nonmajor clinically relevant bleeding compared with warfarin.[170]

Noncardiovascular Surgery

Studies examining outcomes among NOAC users after noncardiovascular surgery largely grouped patients into cohorts spanning minor to major high-risk surgery.[48,103,164,171] NOACs do not increase the rate of postoperative bleeding events when compared with warfarin. A pooled analysis of dabigatran phase III trial bleeding data demonstrated no difference in postoperative bleeding events between patients on dabigatran and warfarin.[171] In the ARISTOTLE trial, there was no difference in stroke, myocardial infarction, mortality, or bleeding for patients on apixaban versus warfarin for NVAF.[105] However, small differences may not have been detected as only 2.9% of procedures in this trial were considered emergent and only 10.2% of procedures were considered major.

Bridging therapy is not recommended during NOAC therapy interruption for patients undergoing surgery. The dabigatran RE-LY study demonstrated an increased risk for major bleeding with bridging therapy.[165] Nonbridged patients had a thromboembolic event risk of 0.6%. Analysis of periprocedural dabigatran use in the RE-LY trial demonstrated no difference in major bleeding events between urgent versus elective surgery and major versus minor surgery.[103] There was also no difference in fatal bleeding, reoperation as a result of bleeding, or transfusion requirements. There were fewer bleeding events in patients with shorter interruption periods, though this may not be a causal relationship given that shorter interruptions may indicate patients with characteristics of faster drug clearance. In contrast, analysis of the Dresden NOAC registry demonstrated increased risk of bleeding in patients with major procedures.[48] Heparin bridging still did not reduce cardiovascular events and did not statistically affect bleeding risk once the data were adjusted for major versus minor procedures.[48] In the Canadian dabigatran cohort study, none of the 541 patients received preoperative bridging, and only 1.7% of patients received postoperative heparin or low-molecular-weight heparin. Despite this, there was only 1 transient ischemic attack event (0.2%) and no major arterial thromboembolic events. In the ARISTOTLE study, 37.5% of procedures did not require NOAC interruption and 11.7% of patients received bridging anticoagulation.[105]

In phase III trials of NOAC use for VTE prevention in high-bleeding-risk orthopedic surgery, the first prophylactic dose was administered 6 to 12 hours postoperatively.[172] Real-world registries of NOAC use after orthopedic surgery suggest higher rates of bleeding

compared with those observed in the trials. In the Dresden NOAC registry, 6 out of 42 patients undergoing major orthopedic surgery developed major cardiovascular (n=2) or bleeding events (n=4).[48] In the Canadian dabigatran cohort, 5 out of 19 patients undergoing major orthopedic surgery developed major bleeding complications.[164] Caution should be exercised in managing patients on NOACs who require major orthopedic interventions.

Neuraxial Anesthesia

Spinal or epidural hematoma can be a devastating complication of neuraxial anesthesia. There are limited data pertaining to the interval between the discontinuation of NOACs, the neuraxial anesthesia procedure itself, and subsequent resumption of the NOAC. Rivaroxaban to prevent VTE after total knee joint replacement or total hip arthroplasty with neuraxial anesthesia has also been examined. In an analysis of 4 trials, neuraxial hematoma occurred in only 1 of 4086 patients in the rivaroxaban group and this occurred before drug administration.[173] Of the 2550 patients who underwent neuraxial anesthesia in the rivaroxaban group in a phase IV cohort study, 1 patient developed intraspinal/hemorrhagic puncture.[174] These data suggest that the incidence of neuraxial hematoma is low despite concurrent administration of therapeutic doses of a NOAC.

There are no robust clinical outcomes data to address the timing and safety of NOAC discontinuation and reinstitution. The American Society of Regional Anesthesia and European Society of Regional Anesthesia and Pain Therapy recommend stopping dabigatran 4 to 5 days before neuraxial block.[175] For patients with end-stage renal disease, 6 days off dabigatran is recommended. For patients with high risk of VTE, dabigatran may be administered 12 hours after the pain intervention. This group recommends stopping apixaban and rivaroxaban 3 to 5 days before neuroaxial block, and resuming either drug 12 hours after the pain intervention if the risk of VTE is considered high. No guidance on edoxaban was considered in this document. These recommendations are controversial because discontinuation periods of ≥4 days are inconsistent with the return to hemostasis time of these agents, which may expose patients to excess thromboembolic risk.

CONCLUSION

NOACs are no longer novel and are now commonly used in day-to-day medical practice. Healthcare providers are encouraged to use well-defined protocols established in collaborations with multiple professional disciplines to address NOAC dose and continuation or cessation when invasive procedures are required. Such protocols should also be encouraged to assist acute care providers who manage bleeding while patients take NOACs. Simple to administer antidotes are either approved for use, such as idarucizumab for dabigatran, or are currently under investigation. Further studies that measure clinical outcomes after NOAC reversal are needed to optimize protocols for NOAC-associated bleeding and periprocedural NOAC management.

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FOOTNOTES

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*Modest.

†Significant.

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Management of Patients on Non–Vitamin K Antagonist Oral Anticoagulants in the Acute Care and Periprocedural Setting: A Scientific Statement From the American Heart Association

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